

Literature Review for Three Centres Antenatal Care Consensus Guidelines

Urinalysis by dipstick for proteinuria

by: Clinical Practice Improvement Unit, The Royal Women's Hospital

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Urinalysis by dipstick for proteinuria

Conclusion and recommendations

The antenatal guidelines apply to the management of low risk pregnant women.

Does the practice of testing urine for increased proteinuria by dipstick lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than not testing urine (by dipstick) at all?

- Further studies are required to specifically answer this question. There may be improved detection of chronic renal disease, but this is not supported by evidence of improved outcomes (maternal, perinatal or cost).
- Dipstick for proteinuria in the presence of hypertension appears to be of benefit in detection of pre-eclampsia.
- There are cost and safety concerns for routine dipstick testing otherwise.

Does the practice of testing urine (for increased proteinuria) by dipstick throughout pregnancy lead to better detection of pre-eclampsia, other hypertensive disorder and chronic renal disease than no further urinalysis until after 26 weeks?

- Further studies are required to ascertain the value of routine dipstick urinalysis for proteinuria prior to 26 weeks gestation.

Does the practice of women interpreting the results of their dipstick testing lead to worse outcomes (detection of pre-eclampsia, hypertension and chronic renal disease) than if carers interpret the results?

- There is insufficient evidence to not support a guideline for women to self-test.

Does the practice of women interpreting the results of their dipstick testing lead to better satisfaction with care or perceptions of the procedure than if carers interpret the results?

- There is no new evidence to support or discourage the practice of women interpreting their own urine dipstick results in terms of perceptions of care.

Literature Search and Appraisal

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Literature Search and Appraisal

1. Introduction

The Three Centres Collaboration contracted the Royal Women's Hospital (RWH) Clinical Practice Improvement Unit to conduct a comprehensive search and critical appraisal of publications addressing the topic of urinalysis by dipstick for proteinuria published between January 2000 and January 2005, to inform the proposed review of the 2001 Three Centres Consensus Guidelines on Antenatal Care.

This literature review should be read in conjunction with the Guideline for antenatal screening for asymptomatic bacteriuria.

2. Topics to be addressed

- 2.1 Does the practice of testing urine for increased proteinuria by dipstick lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than not testing urine (by dipstick) at all?
- 2.2 Does the practice of testing urine (for increased proteinuria) by dipstick throughout pregnancy lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than no further urinalysis until after 26 weeks?
- 2.3 Does the practice of women interpreting the results of their dipstick testing lead to worse outcomes (detection of pre-eclampsia, hypertension and chronic renal disease) than if carers interpret the results?
- 2.4 Does the practice of women interpreting the results of their dipstick testing lead to better satisfaction with care or perceptions of the procedure than if carers interpret the results?

3. Methods

3.1 Search strategy

- The OVID interface was used to search the following electronic databases:
 - MEDLINE: 2000 – January 2005
 - CINAHL: 2000 – January 2005
 - EBM Reviews: June 2000 – January 2005
- Cochrane Database: 2005 Issue 1
- Review of article citations and Cochrane Library references for additional citations
- Guidelines developed by specific Colleges of Obstetricians and Gynaecologists were searched including:
 - Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
 - Royal College of Obstetricians and Gynaecologists (RCOG)
 - Society of Obstetricians and Gynaecologists Canada (SOGC), and
 - American College of Obstetricians and Gynecologists.
- Guidelines developed by other groups were searched for via the internet, on the: United States National Guidelines Clearinghouse, and TRIP database.

3.2 Search terms

Terms used to identify relevant citations are outlined in Appendix I. The search was conducted in three sections:

- Pregnancy/antenatal
- Dipstick
- Satisfaction

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4. Search findings

4.1 Initial search

During the initial search citations were screened and selected using the following inclusion and exclusion criteria:

Inclusion criteria

2000-2005
proteinuria
albuminuria
2-24 hour urine collection

Exclusion criteria

Other medical conditions (malaria, diabetes, hydronephrosis)
Chronic conditions (alcoholism, inflammatory bowel disease, epilepsy, burns, back pain, bipolar disorder, breast cancer, asthma)
Preterm labour
Postnatal
Asymptomatic bacteriuria screening
Pregnancy test
UTI
HELLP syndrome
Severe pre-eclampsia
Blood glucose monitoring
Anticoagulant management

The initial search retrieved 125 citations and 8 guidelines (Appendix II).

4.2 Key citation selection

These citations were triaged into those:

- Possibly containing relevant evidence or authoritative opinion (48 publications – Appendix III), and
- Unlikely to contain relevant evidence or authoritative opinion (85 publications). These were not considered further.

The abstracts and publications from the 48 citations were retrieved and further screened to identify those studies with respect to quality of methodology and relevance to Australian obstetric practice. As a result of this exercise 20 articles were classified as key citations, and were subjected to systematic critical appraisal by the Project Team (Appendix IV).

The evidence within these 20 key citations fell into the following levels (see Appendix IV for definitions):

- Level I evidence: 0 publications
- Level II evidence: 0 publications
- Level III evidence: 15 publications
- Level IV evidence: 3 publications, and
- One letter

4.3 Grading recommendations

The Project Team has adapted the Scottish Intercollegiate Guidelines Network (SIGN) system applying the NHMRC Levels of Evidence, to grade recommendations as follows:

- A At least one meta analysis, systematic review, or RCT directly applicable to the target population; or Levels I or II evidence.
- B A body of evidence including studies rated as Level III-1 or III-2, directly applicable to the target population and demonstrating overall consistency of results.
- C A body of evidence including studies rated as III-3 directly applicable to the target population and demonstrating overall consistency of results.
- D Evidence Level IV.

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5. Results of the critical appraisal process: Commentary on and interpretation of publications reviewed

5.1 Does the practice of testing urine for increased proteinuria by dipstick lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than not testing urine (by dipstick) at all?

The Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) Consensus statement¹ and the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines² state that dipstick for proteinuria is a screening test only with very high false positive rates and recommend that dipstick proteinuria should always be confirmed with either 24 hour urine collection or spot protein creatinine ratio. In addition, RCOG comment that the considerable observer error in dipstick urinalysis for proteinuria can be overcome by automated readers with significantly improved false positive and false negative rates. New devices should be routinely tested for accuracy and predictive values before being introduced into clinical practice.

The RCOG Evidence Based Guidelines for Antenatal Care³ recommend routine dipstick urinalysis for protein at every antenatal assessment where blood pressure is taken, but conclude that further research is required to determine the role of screening for proteinuria.

One significant Australian study evaluated the outcomes for 1000 antenatal women with routine dipstick urinalysis throughout pregnancy. They concluded that in the absence of hypertension routine dipstick urinalysis during pregnancy did not result in better detection of pre-eclampsia. Six women developed proteinuria prior to development of hypertension, half of whom had recognized risk factors for pre-eclampsia. They comment that their study was underpowered for significant maternal and perinatal outcomes but question the benefit of the detection of 3/1000 with proteinuria in whom pre-eclampsia would be diagnosed at a subsequent antenatal visit⁴.

Murphy and Redman comment that this potentially leaves proteinuria undetected for up to 4 weeks between antenatal visits and reinforces the need for randomized controlled data powered to detect relevant maternal and perinatal outcomes⁵.

Regarding the detection of chronic renal disease, an Australian population study by Chadban revealed a prevalence of 16% in a non-pregnant mix-gender cohort⁶.

No evidence was identified to support routine screening in young adults for proteinuria to detect chronic renal disease⁷. In addition, Boulware found it is not cost effective to screen for chronic renal disease in a low risk population⁸.

There are two studies that support dipstick urinalysis to detect proteinuria when hypertension has been diagnosed^{9, 10}. Phelan refines this further by revealing that dipstick proteinuria $\geq 2+$ improves overall diagnostic accuracy of pre-eclampsia at the expense of a false negative rate (7 percent for 'nil', 14 percent for 'trace' and 9 percent overall). This study confirms the need to further investigate dipstick proteinuria with tests such as protein creatinine ratio or timed urine collection in all hypertensive women¹⁰.

There is a significant correlation between a formal 24 hour total protein excretion and 2 hour urinary protein quantification^{11, 12}.

Waugh et al described a reference range for urinary microalbumin/creatinine ratios in uncomplicated pregnancy¹³. A number of recent papers support the use of albumin creatinine ratio during normal pregnancy and preeclampsia to significantly reflect the

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24 hour urinary protein excretion^{14, 15, 16, 17}. However, the largest study to date evaluating 220 women with suspected preeclampsia (≥ 24 gestation) concluded that “PCR does not exclude adequately the presence of significant proteinuria or predict significant proteinuria and should not be used as an alternative to 24 hour urinary protein evaluation”¹⁸.

The accuracy of dipstick in detection of proteinuria may be further improved by the use of automated testing devices¹⁰. However, further evaluation of this is recommended.

Project Team Recommendations (B)

Further studies are required to specifically answer this question.

There may be improved detection of chronic renal disease, but this is not supported by evidence of improved outcomes (maternal, perinatal or cost).

Dipstick for proteinuria in the presence of hypertension appears to be of benefit in detection of pre-eclampsia. There are cost and safety concerns for routine dipstick testing otherwise.

5.2 Does the practice of testing urine (for increased proteinuria) by dipstick throughout pregnancy lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than no further urinalysis until after 26 weeks?

The evidence is not conclusive. When dipstick urinalysis for proteinuria is undertaken at the first antenatal assessment there is a possibility of improved detection of chronic renal disease¹⁹.

Project Team Recommendation (B)

Further studies are required to ascertain the value of routine dipstick urinalysis for proteinuria prior to 26 weeks gestation.

5.3 Does the practice of women interpreting the results of their dipstick testing lead to worse outcomes (detection of pre-eclampsia, hypertension and chronic renal disease) than if carers interpret the results?

One recent study concludes women interpreting the results of their dipstick urinalysis have an equivalent false negative and higher false positive detection rate than of dedicated midwifery / nursing staff performing the same test. However, the authors suggest women self testing of urine during the antenatal phase can be:

- practicable
- easily implemented
- taught to women using verbal instructions at their first antenatal clinic visit
- less confusing for women if the dipstick tests only for protein (not a multiple analysis dipstick), and
- checked or retested by a trained member of staff if there is significant proteinuria (1+ or more)²⁰.

There is no evidence regarding outcomes for mother and baby.

Project Team Recommendation (B)

There is insufficient evidence to not support a guideline for women to self-test.

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5.4 Does the practice of women interpreting the results of their dipstick testing lead to better satisfaction with care or perceptions of the procedure than if carers interpret the results?

There was no new evidence identified.

Project Team Recommendation

There is no new evidence to support or discourage the practice of women interpreting their own urine dipstick results in terms of perceptions of care.

6. Conclusions and recommendations following the literature search and appraisal

The antenatal guidelines apply to the management of low risk pregnant women.

6.1 Does the practice of testing urine for increased proteinuria by dipstick lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than not testing urine (by dipstick) at all?

- Further studies are required to specifically answer this question.
- There may be improved detection of chronic renal disease, but this is not supported by evidence of improved outcomes (maternal, perinatal or cost).
- Dipstick for proteinuria in the presence of hypertension appears to be of benefit in detection of pre-eclampsia. There are cost and safety concerns for routine dipstick testing otherwise.

6.2 Does the practice of testing urine (for increased proteinuria) by dipstick throughout pregnancy lead to better detection of pre-eclampsia, other hypertensive disorder and chronic renal disease than no further urinalysis until after 26 weeks?

- Further studies are required to ascertain the value of routine dipstick urinalysis for proteinuria prior to 26 weeks gestation.

6.3 Does the practice of women interpreting the results of their dipstick testing lead to worse outcomes (detection of pre-eclampsia, hypertension and chronic renal disease) than if carers interpret the results?

- There is insufficient evidence to not support a guideline for women to self-test.

6.4 Does the practice of women interpreting the results of their dipstick testing lead to better satisfaction with care or perceptions of the procedure than if carers interpret the results?

- There is no new evidence to support or discourage the practice of women interpreting their own urine dipstick results in terms of perceptions of care.

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Appendix I

Search framework

A structured approach was used to identify an appropriate search strategy for this topic. Using the Patient/Intervention/Compared with/Outcome (PICO) format search terms were listed and entered into the various electronic databases.

- P All pregnant women
 I Testing urine for proteinuria by dipstick throughout pregnancy
 C Not testing urine
 Testing urine after 26 weeks gestation
 Results interpreted by women/carer
 O Detection of:
 pre-eclampsia
 hypertensive disorders, and
 chronic renal disease
 Satisfaction with care

Search findings

Term	Medline	Premedline	CINAHL	EBM
Pregnancy / pregnancy / antenatal / prenatal / prenatal care / prenatal diagnosis	78886	5863	16649	4110
Pregnancy / pregnancy / antenatal / prenatal / prenatal care / prenatal diagnosis + Proteinuria	17/399	4/34	3/35	2/55
Pregnancy / pregnancy / antenatal / prenatal / prenatal care / prenatal diagnosis + urinalysis / urine test / dipstick / reagent strips / reagent kits diagnostic	24/204	1/6	1/11	0/24
Dipstick/reagent strips / reagent kits diagnostic + chronic renal disease / kidney failure	4/19	0/1	0	0/1
Dipstick/reagent strips / reagent kits diagnostic + preeclampsia	*10/15	0/2	0/2	0
Dipstick/reagent strips / reagent kits diagnostic + hypertension	4/41	2/8	1/4	0/12
Dipstick/reagent strips / reagent kits diagnostic + self test / self care	1/70	0	0/6	0/1
Satisfaction / personal satisfaction + self test / self care	6/170	0	1/107	0/58

Cochrane

	Systematic Review	Central register	DARE
Pregnancy / antenatal / pregnant / prenatal + proteinuria	0/35	2/90	0/4
Pregnancy / antenatal / pregnant / prenatal + urinalysis / urine test / dipstick / urine screen / urine dipstick	0/172	0/124	0/10

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Appendix II Results of Initial Search

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Appendix IV Key Citations

Levels of Evidence Ratings

- I** Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II** Evidence obtained from at least one properly-designed randomised controlled trial.
- III-1** Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
- III-2** Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
- III-3** Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
- IV** Evidence obtained from case series, opinions of respected authorities, descriptive studies, reports of expert committees and case studies.

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2.1 Does the practice of testing urine for increased proteinuria by dipstick lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than not testing urine (by dipstick) at all?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Murray, Homer et al (2002)	4	St George Hospital, Sydney, Australia. March-November 1999. 1000 women enrolled at first antenatal visit. 913 completed the study.	Dipstick urinalysis.	Diagnosis of gestational hypertension, pre-eclampsia, pre-eclampsia superimposed on chronic hypertension.	<p>Of the 35 women who had dipstick proteinuria at the first antenatal visit, 25 (71%) women had further dipstick proteinuria detected during pregnancy, and two (6%) were diagnosed with pre-eclampsia. "</p> <p>338 (39%) of the 867 women without proteinuria (>1+) on dipstick at the first antenatal visit had proteinuria detected at some time during pregnancy.</p> <p>No statistically significant difference was detected in the proportion of women with and without dipstick proteinuria at their first visit who subsequently developed gestational hypertension in that pregnancy. Six women developed proteinuria before the onset of hypertension. Compared with women with a normal result, although numbers were small, women who had an abnormal midstream urine test at their first visit, were more likely to have a urinary tract infection diagnosed during pregnancy.</p> <p>Authors conclude "in the absence of hypertension, routine urinalysis during pregnancy is a poor predictor of pre-eclampsia. Therefore, after an initial screening urinalysis, routine urinalysis could be eliminated from antenatal care without adverse outcomes for women" (p477).</p> <p>Authors recommendations:</p> <ul style="list-style-type: none"> • All low risk women provide an MSU at their first antenatal visit for an automated dipstick urine test. • Women with normal results of a booking dipstick urinalysis require no further urine tests in pregnancy, unless they develop hypertension or clinical signs and/or symptoms of urinary tract infection. • Women with abnormal results of a dipstick urinalysis should have an MSU sent for microscopic examination, culture and sensitivity. • Women found to have true proteinuria and/or haematuria at the first antenatal visit may have underlying renal disease, which should be investigated. • Routine urinalysis should continue for women with 'at-risk' 	Prospective observational study	III-2

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pregnancies, as the detection of pre-eclampsia is important in this high-risk group (p480).

Chadban, Briganti et al (2003)	6	Monash Medical Centre, Australia. May 1999-December 2000 11247 Australians (nationwide population based study) aged ≥ 25 years. Random selection using stratified, cluster method.	Tested for proteinuria, haematuria and GFR.	Prevalence of proteinuria (spot urine protein:creatinine ≥ 0.20 mg/mg) haematuria (spot dipstick $\geq 1+$) confirmed by microscopy (>10000 red blood cells/ml).	Proteinuria was detected in 2.4% of cases (95% CI: 1.6%, 3.1%) and haematuria in 4.6% (95% CI: 3.8%, 5.4%). Approximately 16% had at least one indicator of kidney damage. Age, diabetes mellitus, and hypertension were independently associated with proteinuria, age, gender, and hypertension with haematuria. Authors conclude "approximately 16% of the Australian adult population has either proteinuria, haematuria, and/or reduced GFR, indicating the presence of kidney damage" (pS131).	Population based study	III-2
Topham, Jethwa et al (2003)	7	Leicester General Hospital, Leicester, United Kingdom. 1996-1997. 3808 university students enrolled, data for 3570 included.	Dipstick test for haematuria and/or proteinuria.	Presence of significant renal tract pathology as assessed by presence of urine abnormalities. Added value of screening for haematuria and/or proteinuria.	Screening: 238 (6.3%) provided no specimen; 220 (6.2%) had positive test for blood or protein (135 (3.8%) proteinuria, 62 (1.7%) haematuria, 23 (0.6%) both. Of the 220, 40 had a positive second test, 132 had no subsequent abnormality and 48 provided no second sample. Prevalence: 16 had persistent proteinuria. 14 had persistent microscopic haematuria. 8 had persistent proteinuria and haematuria of whom 3 had underlying renal disease. The study findings do not support routine screening for proteinuria or haematuria in young adults. However, authors recommend the finding of a combination of haematuria and proteinuria as a predictor for renal disease.	Cohort study	III-2
Phelan, Brown et al (2004)	10	St George Hospital, Sydney, Australia. 2000-2001 170 hypertensive	503 samples of midstream urine tested by dipstick compared with automated	Urinalysis protein results compared with spot protein/creatinine ratio (True proteinuria ≥ 30 mg protein/mmol	False positive dipstick tests ranged from 7% at 3+ level to 71% at 1+ proteinuria level compared to false negative rates of 7% for "nil" and 14% for "trace" proteinuria and 9% overall. Accepting the dipstick proteinuria result at face value led to an incorrect diagnosis of pre-eclampsia or gestational hypertension in 85 (50%) women.	Prospective study	III-2

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		pregnant outpatients and inpatients over 9 month period.	urinalysis.	creatinine). Culture and sensitivity if indicated.	<p>Dipstick proteinuria was significantly more likely to be correct (true positive/true negative) if diastolic blood pressure was elevated > 90 mmHg (p = 0.032) and in the absence of ketonuria (p = 0.001).</p> <p>Accepting a diagnosis of pre-eclampsia on the basis of de novo hypertension and dipstick testing alone was accurate less often (70%) when > 1 + was used as a discriminant value than at the 82% of presentations when > 2 + was used (p = 0.001)."</p> <p>Authors conclude "accepting 'ni' or 'trace' proteinuria as a true negative dipstick results fails to identify approximately 1 in 11 hypertensive pregnant women with true proteinuria, a false negative rate that may be acceptable provided these women are subject to ongoing vigilant clinical review. Even with automated urinalysis the false positive rate for dipstick levels >= 1 + is very high, particularly in the presence of ketonuria and relying on this alone to diagnose pre-eclampsia leads to significant errors in diagnosis. Accepting >= 2 + dipstick proteinuria improves overall diagnostic accuracy for pre-eclampsia at the expense of a higher false negative rate. This study emphasizes the need to confirm dipstick proteinuria with a further test such as a spot urine protein/creatinine ratio in all hypertensive pregnant women, particularly in research studies" (p136).</p>		
Evans, Lensmeyer et al (2000)	11	Sinai Samaritan Medical Center, Milwaukee, Wisconsin, USA. 18 month period. 59 pregnant inpatients who were evaluated for renal function were enrolled. Data was analysed on 51.	2 hour urine collection.	Protein excretion by Protein:Creatinine Ratio and 24 hour urine measurements.	<p>Total proteinuria was calculated by protein/creatinine (P:C) ratio. Results in the 2-hour group correlated with the total protein measured in the 24-hour group (1,840.8 +/- 786 and 1,944 +/- 1,060 mg [mean +/- SE], respectively, r2 = 0.95, P < 0.0001).</p> <p>Results for creatinine clearance also correlated in the 2 and 24-hour groups (111 +/- 42 and 122.5 +/- 50 ml/min, respectively; r2 = 0.73, P < 0.001).</p> <p>Authors conclude "two-hour urine sampling offers the same clinical information as 24-h urine collection for the evaluation of renal function" (p233).</p>	Prospective longitudinal study	III-2
Somanathan, Farrell et	12	Royal Hallamshire Hospital, Sheffield,	2 hour urine	Estimated 24 hour	Mean 24 hour protein level was 0.84g (95% CI 0.5-1.2) and the	Prospective observational	III-2

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al (2003)		United Kingdom.	protein level.	protein level.	mean 2 hour level 0.14g (95% CI 0.06-0.2).	study
		February-May 2002.			15 cases had significant proteinuria detected on 24 hour assessment (>0.3g), a sensitivity of 50% for dipstick proteinuria.	
		30 women assessed for proteinuric hypertension >26 weeks gestation.			20 (66%) had 2 hour protein levels >0.025g. 16 of these had confirmed proteinuria on 24 hour collection (sensitivity 80%). Pearson's correlation coefficient was 0.76 (<i>P</i> 0.000), suggesting moderate correlation between the 24 hour and the 2 hour protein levels."	
					Authors conclude the comparison between the dipstick analysis and 2 hour estimation demonstrates clearly a much greater sensitivity for the 2 hour estimation >0.025g (50% versus 80%) for significant 24 hour protein and therefore the 2 hour sample may have a place in a day case setting.	
Waugh, Bell et al (2003)	13	Leicester Royal Infirmary, United Kingdom.	(Micro)albumin / creatinine ratio (ACR) on fresh, mid-stream first void early morning urine sample.	Gestation specific reference range in an uncomplicated pregnancy, for: <ul style="list-style-type: none"> urinary microalbumin excretion creatinine concentration ACR 	<ul style="list-style-type: none"> 95% reference ranges are plotted for urinary microalbumin concentration, creatinine concentration and ACR in uncomplicated pregnancy. There is a significant increase (<i>P</i> =0.016) in the ACR in the third trimester. The mean difference is 0.091 mg of albumin/mmol of creatinine (95% confidence interval, 0.014-0.168). 	Prospective cross-sectional study
		482 women from the antenatal clinic population. Data was analysed on 447 women.				
		Excluded if a history of pre-existing proteinuria, hypertension, renal disease, diabetes, preeclampsia or non-Caucasian. Also excluded if they developed hypertension, significant proteinuria or gestational diabetes or birthed				

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		≤ 36 weeks gestation.					
Risberg, Larson et al (2004)	14	Sweden antenatal clinics at: <ul style="list-style-type: none"> • University Hospital, Uppsala (high risk), • 5 urban • one in Ornskildsvik . <p>65 pregnant women</p>	Measurement of urine albumin / creatinine ratio in spot samples.	Correlation to results of 24 hour urine collections during pregnancy.	<ul style="list-style-type: none"> • 24 hour urine collections in weeks 12, 24 and 36 of pregnancy from both normotensive women and women who developed hypertension or who had pregnancy-induced hypertension (PIH) when they entered the study. • 24 hour albumin excretion was significantly correlated to the albumin/creatinine ratio in all measurements (Pearson correlation coefficient). • 12 weeks: the values in the normotensive group were $n = 44$, $r = 0.964$, $p < 0.001$; and in the PIH group $n = 8$, $r = 0.789$, $p < 0.05$. • 24 weeks: the correlation values were $r = 1.0$ and $p < 0.001$ in both the normotensive group ($n = 41$) and in the PIH group ($n = 11$). • 36 weeks: the correlation values in the normotensive group were $n = 39$, $r = 0.791$ and in the PIH group $n = 16$, $p < 0.001$ and $r = 1.0$ and $p < 0.001$. • Microalbuminuria is urine albumin excretion higher than 30 mg/24 hours and this corresponded to an albumin/creatinine ratio of 2.9. Microalbuminuria was found in three persons in the PIH group and in two persons in the normotensive group. • One of the 46 normotensive women (2%) had overt albuminuria (> 300 mg/24 h) and 3 of the 19 PIH women (16%). In all these women the high albumin values had been detected by using the albumin/creatinine ratio method. <p>Authors conclude that during pregnancy albumin excretion in urine correlates significantly to the albumin/creatinine ratio. In addition, the urinary albumin/creatinine ratio appears to be a good option to the dipstick method and to 24-h urine collections.</p>	Prospective longitudinal study	III-2
Neithardt, Dooley et al (2002)	15	Northwestern Memorial Hospital, Chicago, USA. May-November 2000. 36 women admitted to the antenatal unit and undergoing a 24	Single voided protein-to-creatinine (P:C) ratio.	Validate the prediction of 24 hour protein excretion.	<ul style="list-style-type: none"> • There was a significant correlation between the 24-hour urine protein excretion and the P:C ratio ($r = 0.93$, $P < .001$). • There were weak and not significant associations of maternal age and gestational age at collection with P:C ratio and 24-hour urine protein. • Compared with multiparous women, there was nonsignificant trend of higher P:C ratios and 24-hour urine protein in nulliparous women. • There was no confounding effect of maternal age, gestational age, or parity on the basis of multiple linear 	Prospective cohort study	III-2

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		hour urine collection for the quantitation of proteinuria. Data was analysed on 30 women.			<p>regression.</p> <ul style="list-style-type: none"> In all of the eight women who had serial paired urine collections performed, the trend of increasing or decreasing 24-hour urine protein excretion was predicted by the P:C ratio. <p>Authors conclude the data supports the use of single voided P:C ratio for hospitalized pregnant women to predict the 24-hour urine result. In addition, the P:C ratio appears to predict trends in protein excretion over time.</p>		
Yamasmit, Wongkitisophon et al (2003)	16	King Chulalongkorn Memorial Hospital, Bangkok, Thailand (tertiary centre).	Random urinary protein: creatinine ratio.	Correlation with the 24 hour urine measurement of protein.	<ul style="list-style-type: none"> There was a strong correlation between the random urinary protein-to-creatinine ratio and the quantitation of 24-hour proteinuria ($r = 0.929$, $p < 0.001$) in hospitalized pregnant patients with preeclampsia. 	Cross-sectional descriptive study	III-2
		32 women diagnosed with preeclampsia and admitted to antenatal ward. Data was analysed on 25 women.					
Yamasmit, Chaithongwongwatthana et al (2004)	17	King Chulalongkorn Memorial Hospital, Bangkok, Thailand (tertiary centre).	Random mid stream urine sample for protein-to-creatinine ratio determination.	Correlation with the 24 hour urine measurement of protein.	<ul style="list-style-type: none"> 69% of the study population had significant proteinuria. A cutoff of 0.19 demonstrated a sensitivity of 100%, a specificity of 53.8%, positive predictive value of 82.9% and negative predictive value of 100%. Significant proteinuria was ruled out with a ratio below 0.22. The optimal cutoff value is 0.25 which yielded sensitivity, specificity and accuracy of 96.6%, 92.3% and 95.2% respectively. <p>Authors conclude that for hospitalized preeclamptic patients, the "random urinary protein-to-creatinine ratio at a cutoff of 0.25 revealed a highly accurate prediction of significant proteinuria and could be a more practical alternative for assessment of proteinuria".</p>	Prospective cohort study	III-2
		July 2002- February 2003					
		55 pregnant women admitted with a suspicion of preeclampsia. Excluded women with renal disease or UTI. Data was analysed on 42.					

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Durnwald, Mercer (2003)	18	<p>MetroHealth Medical Center, Ohio, USA (tertiary centre)</p> <p>January 2001-July 2002.</p> <p>220 women investigated for suspected preeclampsia at 24 or more weeks gestation. No concurrent diagnosis of chronic hypertension, diabetes or renal disease.</p>	<p>Protein/creatinine ratio followed by 24 hour urine collection</p>	<p>The value of protein/creatinine ratio for significant (>or=300 mg) and severe proteinuria (>or=5000 mg) based on 24-hour urine total protein:</p> <ul style="list-style-type: none"> • Positive predictive values • Negative predictive values • Sensitivity, and • Specificity. 	<ul style="list-style-type: none"> • On 24-hour urine evaluation 76.4% developed significant proteinuria (8.2% developed severe proteinuria). • Regression analysis of protein/creatinine ratio and 24-hour urine total protein level showed a poor correlation ($r(2)=0.41$). • Receiver operator characteristic analysis revealed an area under the curve of 0.80, but the shoulder value of 390 mg/g carried a high false-negative rate (45.2%). With a more conservative cutoff value, a protein/creatinine ratio of >or=300 mg/g had a: <ul style="list-style-type: none"> ○ Poor negative predictive value (47.5%) ○ Specificity for significant proteinuria (55.8%), ○ Positive predictive value of 85.5%, and ○ Sensitivity of 81%. <p>For severe proteinuria, a protein/creatinine ratio of >or=5000 mg/g had a:</p> <ul style="list-style-type: none"> ○ Poor positive predictive value (61.9%) ○ Sensitivity (72.2%) ○ Negative predictive value of 97.5%, and ○ Specificity of 96.0%. <p>Authors conclude "protein/creatinine ratio does not exclude adequately the presence of significant proteinuria or predict severe proteinuria and should not be used as an alternative to 24-hour total protein evaluation" (p 848).</p>	Prospective cohort study	
Barton, O'Brien et al (2001)	9	<p>Central Baptist Hospital, Lexington, USA.</p> <p>February 1995-February 1998.</p> <p>748 women with a singleton pregnancy between 24-35 weeks' gestation who had no proteinuria by dipstick at enrolment.</p>	<p>Dipstick urinalysis for proteinuria on the first two days of outpatient care.</p>	<p>Progression to proteinuria.</p> <p>Progression to pre-eclampsia.</p> <p>Secondary outcomes: rate of progression to severe pre-eclampsia; obstetric complications; and neonatal outcomes.</p>	<p>Proteinuria developed in 343 of the 748 (46%) women.</p> <p>Severe pre-eclampsia developed in 72 of the 748 women (9.6%).</p> <p>There were no significant differences in demographic characteristics between those women in whom persistent proteinuria developed and those in whom it did not develop.</p> <p>Authors conclude, of those women who develop mild gestational hypertension prior to term, 46% ultimately had pre-eclampsia, with progression to severe disease in 9.6%. The development of proteinuria is associated with an earlier gestational age at delivery, lower birth weight, and an increased incidence of small-for-gestational age newborns.</p>	Secondary analysis of a prospective cohort	III-3

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Boulware, Jaar et al (2003)	8	American population based study of adults aged 50 years (52% female, 80% non-Hispanic white, 11% non-Hispanic black, 5% Mexican American) presenting to General Practitioner for annual assessment. No previous proteinuria.	Urine dipstick test for proteinuria.	Cost per quality-adjusted life year (QALY).	<p>Where individuals had no hypertension or diabetes, the cost-effectiveness ratio for screening vs no screening (usual care) was unfavorable (282 \$818 per QALY; incremental cost of \$616 and a gain of 0.0022 QALYs per person). However, screening such persons beginning at age 60 years yielded a more favorable ratio (\$53 372 per QALY).</p> <p>Screening those with hypertension made the ratio highly favorable (\$18 621 per QALY; incremental cost of \$476 and a gain of 0.03 QALYs per person). Chronic kidney disease progression and death prevention benefits mediated the cost-effectiveness.</p> <p>Authors suggest “Influential parameters that might make screening for the general population more cost-effective include a greater incidence of proteinuria, age at screening (\$53 372 per QALY for persons beginning screening at age 60 years), or lower frequency of screening (every 10 years: \$80 700 per QALY at age 50 years; \$6195 per QALY at age 60 years; and \$5486 per QALY at age 70 years)” (p 3101).</p> <p>Authors conclude “early detection of urine protein to slow progression of chronic kidney disease and decrease mortality is not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) or conducted at an infrequent interval of 10 years” (p3101).</p>	Cost effectiveness analysis (Markov decision analytic model)
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2.2 Does the practice of testing urine (for increased proteinuria) by dipstick throughout pregnancy lead to better detection of pre-eclampsia, other hypertensive disorders and chronic renal disease than no further urinalysis until after 26 weeks?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Murakami, Masahiro et al (2000)	19	Nishisaitama-Chus National Hospital, Wakasa, Saitama, Japan. 1980-1999. 86 Japanese women hospitalized and who had: <ul style="list-style-type: none"> • severe hypertension and/or • severe proteinuria and • kidney biopsy. 	Postpartum needle biopsy of kidneys.	Diagnosis of underlying renal disease.	<p>19 (22.1%, 95% confidence interval [CI] 13.9%, 32. 3%) were diagnosed with underlying renal disease. Those with renal disease had a significantly earlier onset of proteinuria than those without (median 11 versus 32 weeks' gestation, P <.001).</p> <p>18 of the women with renal disease had proteinuria, hypertension, or both before 30 weeks' gestation.</p> <p>Ten of 12 women with severe gestational proteinuria (83.3%, 95% CI 51.6%, 97.9%) had underlying renal disease. In women with severe pre-eclampsia, onset before 30 weeks' gestation was the best predictor of underlying renal disease (odds ratio 34.1, 95% CI 3.8, 304.5).</p> <p>There were lower rates of severe hypertension (nine of 19 versus 59 of 67, P <.01) and small-for-gestational-age infants (four of 19 versus 34 of 67, P <.05) in women with renal disease than those without renal disease.</p> <p>Authors conclude "women who had gestational proteinuria or pre-eclampsia before 30 weeks' gestation were more likely to have had underlying renal disease" (p945).</p>	Retrospective review/cohort	III-2

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2.3 Does the practice of women interpreting the results of their dipstick testing lead to worse outcomes (detection of pre-eclampsia, hypertension and chronic renal disease) than if carers interpret the results?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Goh and Krause (2002)	20	Gold Coast Hospital, Queensland, Australia. March 2000. 212 women recruited attending antenatal clinic, 209 included in study.	Women self testing urine using a dipstick.	Proteinuria detection compared with nurse dipstick urinalysis.	The authors conclude that although women tended to overestimate proteinuria, self testing of urine during the antenatal phase can be: <ul style="list-style-type: none"> • practicable • easily implemented • taught to women using verbal instructions at their first antenatal clinic visit • less confusing for women if the dipstick tests only for protein (not a multiple analysis dipstick), and • checked or retested by a trained member of staff if there is significant proteinuria (1+ or more). 	Prospective comparison study	III-2