Clinical Question:

In pregnant women, what is the accuracy, feasibility and utility for self-testing of proteinuria?

Background, Current Practice and Advantages over Existing Technology

Protein leaking into the urine combined with high blood pressure defines pre-eclampsia, a condition affecting 2-8% of pregnancies in the UK (1, 2). Pre-eclampsia can lead to eclampsia; a serious condition with seizures and a high mortality rate (0.83). There are around 300-400 confirmed cases of pre-eclampsia in the UK every year (3). A recent audit of maternal deaths in the UK reported 19 deaths from pre-eclampsia and eclampsia during 2006-2008 indicating that the number of deaths from pre-eclampsia has not fallen since the 1991-1993 report (4).

Diagnosing pre-eclampsia requires monitoring of blood pressure and proteinuria, typically by midwives at intermittent times during pregnancy, generally coinciding with antenatal visits (5). Standard reagent strips are used with further testing in the case of a positive result (24 hour sample testing and spot testing urine protein:creatinine ratio (uPCR) as per NICE and PRECOG guidelines) (6, 7). Meta-analysis has shown that the uPCR optimum threshold is between 0.3-0.35mg/mmol and this provides a sensitivity and specificity of above 0.75 (8). Values in excess of 150 mg/L or 300 mg/24 hr during pregnancy are usually associated with either pre-eclampsia or underlying renal disease. Routine care appears to be similar in the U.S.A: the recent American congress of obstetricians and gynaecologists (ACOG) guidelines suggest that a dipstick reading of 1+ suggests proteinuria, but should only be used when quantitative methods are not available (ACOG 2013). The report recommended weekly proteinuria testing and weekly, or home BP monitoring in hypertensive pregnancy, suggestive of a move towards home monitoring. The development of proteinuria in a hypertensive pregnancy is universally agreed to be significant (9).

A significant number of women in the UK develop pre-eclampsia within the interval between antenatal visits (3). Furthermore a significant proportion of deaths from pre-eclampsia also had
serious disease present between normal antenatal visits (10). Regular self-monitoring of blood pressure and self-testing for proteinuria could improve detection of pre-eclampsia in the higher risk pregnant population, as well as reducing the time, cost, stress and inconvenience of frequent appointments without compromising the ability to detect and monitor a potentially serious disease.

Self-testing of urine for glucose or albumin is becoming increasingly common in diabetic care (11, 12). The pregnant population are also well accustomed to urine testing with the use of home pregnancy tests as the standard means of diagnosing pregnancy for women in the UK (13, 14). However, there are surprisingly little data on self-testing of proteinuria in the pregnant population. Several studies describe providing pregnant patients with urine dipsticks to periodically check for protein alongside self-monitoring blood pressure (15-18) but have not formally evaluated test performance, effect on frequency of visits to clinics and pregnancy outcome. Large screening studies have been carried out within the general population (excluding pregnancy) with the aim of improving early detection of renal disease. These studies found that self-testing improved the chances for an early diagnosis and therapy, though the study concluded that participants had a tendency to over diagnose proteinuria (19, 20).

Details of Technology:

Urinalysis reagent strips are visually read tests used to detect protein in urine samples. A large number of urinalysis reagent strips are commercially available, all of which follow a similar testing methodology (Table 1).

The reagent strip is dipped briefly into a fresh, mixed first-pass (non-centrifuged) urine sample, ensuring all test pads are fully immersed. Upon removal, some products state to touch side of strip against container or to blot the strips lengthwise onto absorbent paper to remove excess. At times ranging from 30 seconds to 2 minutes, the reagent areas can be compared to the corresponding colour blocks on the colour chart, giving a semi-quantitative result. An automated reader can also be used to reduce operator/reader variability (21).

The stated sensitivities of these tests range from 50-300mg/L. Normal levels of protein are around 50mg/L in the first and second trimesters and <100mg/L in the third. Values in excess of 150mg/L are associated with either pre-eclampsia, underlying renal disease or a urinary tract injection and correspond to 1+ or greater on the dipstick (9).

There has been limited evaluation of the diagnostic accuracy of dipstick analysis for proteinuria, when performed by health care professionals. A 2004 meta-analysis of studies comparing point of care testing to laboratory testing concluded that the accuracy with a 1+ threshold for predicting proteinuria is poor, with a positive likelihood ratio of 3.5. Accuracy at higher protein thresholds was
not analysed, due to sparse data. This study concluded that significant proteinuria could not be accurately detected or excluded at the 1+ threshold and should not be used to diagnose pre-eclampsia (22).

A prospective study carried out in Australia analysed 503 urine samples from 170 hypertensive pregnant women using an automated dipstick reader found that using a dipstick proteinuria 1+ to diagnose pre-eclampsia provided an overall accuracy of 70% and a false positive rate of 71%. However, a dipstick proteinuria of 2+ provided a significant improvement with an overall accuracy of 82% and false positive rates reduced to 7% at the 3+ level. Interestingly, they reported that incorrect urinalysis by dipstick was significantly more likely (p=0.032) if the blood pressure was below 90mmHg (23).

**Patient Group and Use:**

- Pregnant women

**Importance:**

The incidence of pre-eclampsia is around 5%, and severe pre-eclampsia and eclampsia in the UK are estimated to occur in 5/1,000 pregnancies (24) and 4.9/10,000 pregnancies (3), respectively. Around 6 mothers die each year in the UK from the complications of pre-eclampsia (1, 25). The 8th Confidential Inquiry into Maternal and Child Health (2) found that pre-eclampsia and eclampsia combined were the second leading cause of direct maternal death in the UK, with 19 women dying due to pre-eclampsia between 2006-2008 and the mortality rate is not declining. Furthermore around 1,000 babies die each year in the UK because of the condition, mostly because of complications of early delivery (1).

A significant number of women in the UK have been reported to develop pre-eclampsia during the interval between antenatal visits with 22% of women (64/291 women with complete antenatal records) experiencing their first convulsion while under community care in 1992 (3), furthermore a significant proportion of deaths from pre-eclampsia also had serious disease present between normal antenatal visits (10). Regular home self-testing for proteinuria could improve the detection of pre-eclampsia by increasing screening whilst reducing the burden on primary care of more frequent testing. Self-testing could reduce the stress and inconvenience of frequent additional appointments in high risk women without compromising the ability to detect and monitor a potentially serious disease. It may also act to improve women’s involvement in antenatal care and improve women’s confidence in self-monitored results. Self-testing may also support a gradual move towards telehealth in the NHS as a means of reducing face to face visits and improving efficiency of care (26).
Previous Research:

We evaluated the literature comparing the accuracy and utility of standard proteinuria dipsticks used by a health professional to the same standard dipstick used by pregnant women themselves (self-testing). Three studies were identified, which are outlined below. A search of the clinical trials registry failed to find any on-going clinical trials into the self-testing of proteinuria in pregnancy. The reference standard for assessing proteinuria is a 24 hr laboratory measurement of protein excretion or urine protein-creatinine ratio (uPCR) (7). No reports were identified that directly compared self-testing for proteinuria to laboratory testing.

Accuracy compared to existing technology

A 2002 prospective observational study compared the accuracy of visually read dipstick self-testing for proteinuria by 209 pregnant women to the results of an experienced nurse using the same urine sample (27). All testing was carried out in an antenatal clinic and there was no comparison of the self-testing and nurse testing to 24 hr urine excretion or uPCR.

Women interpreting their dipstick analysis were found to have an equivalent false negative rate (8.6%) and higher false positive rate (35.9%) than of the nurse performing the same test. There was significant difference (p<0.001) between the nurse’s test and the women’ results; however the majority (53%) of differences occurred between a negative protein result and a trace result, from a clinical viewpoint these changes were deemed insignificant. By considering a positive as 1+ or more and a negative defined as 0 or trace, a moderate, but significant difference remained between nurse test and self-test. The authors concluded that the pregnant women tended to overestimate their proteinuria (27).

This study suggests that women self-testing urine during the antenatal phase may be possible and implemented with verbal instructions during antenatal visits, with results being rechecked by a trained health professional if 1+ or more dipstick proteinuria reading was found. The tendency of the pregnant women to overestimate proteinuria could be at least partly addressed by further training; Bell et al (28) illustrated that overestimation of proteinuria largely occurred with the least experienced nursing staff, and that further training, particularly providing instructions to avoid rounding up results (If the colour appears between two categories to use the lower result) as you might expect reduced false positive rates. The authors also suggest that using a dipstick test only for protein (rather than one containing multiple different tests) may be less confusing.

Diagnostic tests for urinary albumin in pregnancy.

Urine albumin tests have been assessed in pregnancy with pooled estimates of sensitivity and specificity for pre-eclampsia have been calculated as follows; for albuminuria 62% (95% CI 23 to 90%) and 68% (95% CI 57 to 77%); albumin-creatinine ratio 19% (95% CI 12 to 28%) and 75% (95% CI 73 to 77%) (29). Furthermore preterm labour, preeclampsia, intrauterine growth restriction (IUGR),
preterm premature rupture of membranes (PPROM) were more common among women with albuminuria (30). This shows great promise for albumin levels to be used in the prediction of pre-eclampsia, however reports so far have been varied and further work is needed to evaluate the predictive power of this test and relationship between albuminuria and pregnancy outcome.(8) Dipsticks for albuminuria have been developed but are not currently part of clinical pathways and have not been tested in pregnancy in the home environment.

**Impact compared to existing technology**

There were no data presented on patient satisfaction or acceptability; however, no women declined to take part and many expressed ‘disappointment’ when the study concluded and the authors noted it would give women a sense of responsibility and control with their own care (27).

Our search identified a conference abstract outlining the results over a 10 year period during which the hospital issued pregnant women (over 26 weeks gestation) a prescription and guidance leaflet on self-testing of urine (31). A cohort of 100 prima gravida cases who developed pre-eclampsia were reviewed to determine the initial method of detection of pre-eclampsia. The article reported that 25% of women were self-referred to hospital, of which 20% were as a result of proteinuria detected on home urine dipstick. No further data was reported and the abstract concluded that the urine dipstick self-testing could be an affordable way of increased testing of proteinuria that could improve detection of disease by self-referral to midwifery staff in the community and in hospital. There is no full publication of this work to date.

A cost analysis study carried out in the U.S.A in 2006 involved 1140 women with gestational hypertension who performed a qualitative urine test twice daily alongside other biometric data (blood pressure, weight, foetal movement) (18). The accuracy of the urine self-testing was not analysed; however in comparison to a hypothetical control group, the admission rate and mean length of stay per patient reduced by 81% and 34%, respectively. Emphasis was placed on the need for at least once daily measurements to be taken, with increased patient education alongside ready access to healthcare providers, and the reliability of the individual.

In terms of efficacy, this study argued that due to the present technology and low rate of complications in asymptomatic mildly hypertensive patients, the essential monitoring required can be performed outside hospital, thereby reducing the need for prolonged hospital visits. Reducing the stress and inconvenience of hospital visits can result in pregnancy prolongation, decreasing short-term neonatal morbidity (32).
Self-monitoring of proteinuria in the general population

A number of studies examined the use of self-testing urine protein in the general population which provide useful insights into potential issues regarding feasibility and acceptability.

The Dutch Kidney Foundation began an albuminuria self-test program in September 2006, whereby adults, via a media campaign, were invited to order a free albuminuria self-test. Cross-sectional analysis indicated that of 71,741 participants, 21% individuals reported a positive result, however only 25% of these visited a GP after self-testing (20). Of the 3,983 participants who visited a GP, 183 individuals were diagnosed with new disease. A further study looked at the influence of this program upon detection of new disease before and after the program; the number of GP consultations increased by 5 per 10,000 in the year following the study, and 2.1 times more patients were diagnosed with urinary diseases, the increase being found particularly in patients with no previous risk factors (33). It is difficult to distinguish in this study the effects of the mass media campaign which may increase awareness generally within the population, from individuals self-testing specifically.

The number of false positives is a key concern regarding the impact of self-testing; three of the studies found (20, 33, 34), attempted to increase the diagnostic value of results by instructing individuals to carry out three self-tests within a week, or with five days in-between; and defining a positive test result as 2 positive tests out of three. However, an evaluation questionnaire study indicated that when a number of the tests were false positives this led to worries amongst patients; this could potentially lead to unnecessary use of health care/medicalisation and unnecessary costs.

Guidelines and Recommendations

There is no mention of self-testing for proteinuria in NICE guidelines for pregnancy care or from NHS England (5, 7). However NICE indicate that further research is needed to determine the role of screening for proteinuria in healthy pregnancy and that there is a need for large, high-quality prospective studies comparing the various methods of measuring proteinuria (automated reagent-strip reading devices, urinary protein:creatinine ratio, urinary albumin:creatinine ratio, and 24-hour urine collection) in pregnant women with new-onset hypertension.

Cost-effectiveness and economic impact:

This simple and cheap test could improve the detection of a potentially serious disease (reducing further care due to early intervention), and could reduce additional appointments (35).
Research Questions:

1. What is the accuracy of self-testing of proteinuria by pregnant women in a home environment compared to nurse/midwife testing, automated readers or laboratory testing?
2. What is the acceptability of self-testing of proteinuria to women and health professionals in the UK?
3. Can self-testing of proteinuria improve detection of pre-eclampsia and/or enhance the decision making process regarding the need for additional or acute midwife appointments either alone or when combined self-monitored BP readings?
4. What is the effect of self-testing of proteinuria on the number of additional antenatal appointments required during pregnancy?
5. Is self-testing of proteinuria a cost effective method of measuring proteinuria in pregnancy? (How does the use of self-testing impact upon the rate of referral/ burden upon the NHS)
6. What is the accuracy of other proteinuria tests such as albuminuria reagent strips when used by pregnant women?

Suggested next step:

1. Studies evaluating acceptability of self-testing for proteinuria in pregnant women among health care professionals.
2. Pilot studies in pregnant women addressing accuracy, acceptability, utility and accuracy of self-testing.

Expected outcomes:

Currently there is insufficient published evidence to draw firm conclusions about the clinical benefit of self-testing of proteinuria in pregnancy. The tendency of pregnant women to overestimate proteinuria combined with the current limitation of the technology in terms of specificity and sensitivity could result in an increased burden upon the healthcare system with minimal effects upon detection and outcome of pregnancies. Moreover, some countries have moved away from using urine proteinuria at all in prenatal care. However if proven to be sufficiently accurate and cost effective, the self-testing of proteinuria (or indeed albuminuria) has the potential to be a valuable method of screening for pre-eclampsia in pregnancy, and may result in earlier diagnosis of this condition than current practice, potentially leading to improved outcomes.
Table 1

Table of devices recommended for home testing

<table>
<thead>
<tr>
<th>Device name/ manufacturer</th>
<th>Approval</th>
<th>Detection limit/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urincheck Health Screen 10 by Express Diagnostics</td>
<td>FDA cleared/ CLIA waived CE not stated</td>
<td>150-300mg/L</td>
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<td>Uristix 4 by Siemens</td>
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</tr>
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<td>Not stated</td>
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<td>Combur SHC test by Roche</td>
<td>FDA cleared/ CLIA waived ( FDA approved for home use) CE marked</td>
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</tr>
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<td>Mission urinalysis reagent strips by Acon laboratories</td>
<td>FDA cleared- CLIA waived CE marked</td>
<td>75-150mg/L</td>
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<td>Phinex 10 parameter urinalysis test reagent strips by Experian Health</td>
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<td>Not stated</td>
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<td>Fisher brand10-5G urine reagent strips by Fisherbrand</td>
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<td>Not stated</td>
</tr>
<tr>
<td>Urige- 3,5,8,9 urine reagent strips by syntron</td>
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<td>Not stated</td>
</tr>
<tr>
<td>Cybow urine reagent strips by DFI</td>
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<td>100-150mg/L</td>
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<tr>
<td>1 parameter protein test URS reagent strip by KIP diagnostics</td>
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<td>150-300mg/L</td>
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Tests recommended for professional use only

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<th>Approval</th>
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<tr>
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References:

1. NHS. (2013) Pre-eclampsia http://www.nhs.uk/conditions/Pre-eclampsia/Pages/Introduction.aspx

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