

**Literature Review
for
Three Centres Antenatal Care Consensus Guidelines**

Antenatal screening for Asymptomatic Bacteriuria

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

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Antenatal screening for Asymptomatic Bacteriuria

Conclusion and recommendations

Does routine screening for asymptomatic bacteriuria during pregnancy (and treatment of those found to be positive) result in improved outcomes (less urinary tract infections, preterm birth and low birth weight) compared with no screening?

The incidence of ASB in pregnancy is 6%. Untreated in pregnancy, ASB risks include pyelonephritis (20%) and preterm birth (10%). Compared with no screening, routine screening for ASB in pregnancy appears to result in improved outcomes of 40% reduced risk of preterm delivery or low-birthweight babies, and 80% reduced risk of development of pyelonephritis. Long-term outcomes have not been thoroughly investigated. This evidence is primarily drawn from existing guidelines. More recent evidence raises concerns regarding the number needed to treat where there is improved perinatal care. Additional concerns are that treatment may be altering the profile of microbiosis.

Recommendation (A)

The routine screening for ASB during pregnancy and treatment of those found to be positive is recommended to improve outcomes with respect to less urinary tract infections, preterm birth and low birth weight.

In pregnant women, which method is more accurate at detecting asymptomatic bacteriuria – dipstick reagent testing or laboratory culturing of a voided MSU specimen?

Culture of voided MSU specimen remains the gold standard for detecting ASB in pregnancy. The drawbacks of urine culture include delay in result availability and cost. Advantages include being able to identify causative organisms and ability to determine antibiotic sensitivities.

Reagent strip testing will detect 50% of women with ASB, and uriscreen (enzymatic test) will detect 60%. The specificity of reagent strip testing of 90% is reassuring in that only 10% of women without ASB will require confirmatory testing with urine culture of a MSU specimen.

Therefore evidence suggests that dipstick testing is a reasonable method of exclusion of ASB as the specificity and negative predictive value in low risk women appears to be in excess of 90%. However, culture remains the gold standard, and should definitely be performed if dipstick testing is positive.

Recommendation (B-C)

Laboratory culturing of a voided MSU specimen is more accurate at detecting ASB in pregnant women.

However, this recommendation should consider the cost and time which may make dipstick reagent testing or enzymatic testing more attractive options for routine screening for ASB in pregnancy.

Is it more cost effective to screen women for asymptomatic bacteriuria using dipstick reagent testing or laboratory culturing of a voided MSU specimen?

It is more cost effective to screen women for ASB, with respect to prevention of preterm delivery, by midstream urine specimen culture. Laboratory culture appears to be more cost effective than dipstick reagent testing due to the poor sensitivity of the dipstick reagent testing of 50%.

Recommendation (C)

It is more cost effective to screen women for ASB with respect to prevention of preterm delivery using laboratory culture rather than dipstick reagent testing.

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Is it more effective to screen for asymptomatic bacteriuria (by the most effective detection method) at booking or only in later pregnancy (after 26 weeks) in terms of urinary tract infections, preterm birth and low birth weight?

Guidelines continue to recommend screening for ASB at 12-16 weeks gestation based on historical evidence. The evidence for this is not explicit. The only relevant new citation identified by the project team found that testing prior to 20 weeks gestation missed over half ASB cases and recommended a culture in each trimester for the greatest detection of ASB. The detection rate for ASB is improved 2-fold with testing each trimester.

This raises issues related to cost, which have not been specifically evaluated in the literature.

Recommendation (C)

The project team agrees with the existing guidelines which continue to recommend screening at 12-16 weeks gestation.

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 antenatal screening for asymptomatic bacteriuria published between January 2000 and March 2005, to inform the proposed review of the 2001 Three Centres Consensus Guidelines on Antenatal Care.

2. Topics to be addressed

- 2.1 Does routine screening for asymptomatic bacteriuria during pregnancy (and treatment of those found to be positive) result in improved outcomes (less urinary tract infections, preterm birth and low birth weight) compared with no screening?
- 2.2 In pregnant women, which method is more accurate at detecting asymptomatic bacteriuria – dipstick reagent testing or laboratory culturing of a voided MSU specimen?
- 2.3 Is it more cost effective to screen women for asymptomatic bacteriuria using dipstick reagent testing or laboratory culturing of a voided MSU specimen?
- 2.4 Is it more effective to screen for asymptomatic bacteriuria (by the most effective detection method) at booking or only in later pregnancy (after 26 weeks) in terms of urinary tract infections, preterm birth and low birth weight?

3. Methods

3.1 Search strategy

- 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), and
 - Society of Obstetricians and Gynaecologists Canada (SOGC).
- Guidelines developed by other groups were searched for via the internet, on the: United States National Guidelines Clearinghouse, and TRIP database.
- The OVID interface was used to search the following electronic databases:
 - MEDLINE: 2003 – January 2005
 - CINAHL: 2003 – January 2005
 - EBM Reviews: June 2003 – January 2005
- Cochrane Database: 2005 Issue 1
- Review of article citations and Cochrane Library references for additional citations

3.2 Search terms

Terms used to identify relevant citations are outlined in Appendix I. In summary, the search was conducted using and combining terms for:

- Asymptomatic bacteriuria / urinary tract infection
- Pregnancy
- Urinalysis
- Cost effectiveness
- Screening

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4. Search findings

4.1 Initial search

Three guidelines were retrieved. The AGREE tool was applied by the project team and as a result the first two were included as key citations.

- Royal College of Obstetricians and Gynaecologists (RCOG). Clinical Guideline: Antenatal care: routine care for the healthy pregnant woman¹.
- United States Preventive Services Task Force (USPSTF). Recommendation statement: Screening for Asymptomatic Bacteriuria².
- Institute for Clinical Systems Improvement (ICSI). Health Care Guideline: Routine prenatal care.

The selected guidelines reduced the search scope to 2003 -2005. In addition to the guidelines, the initial search applied the following inclusion and exclusion criteria to retrieve 68 citations (Appendix II):

Inclusion criteria

2003 – 2005
Antenatal diagnosis

Exclusion criteria

Non – English
Drug dynamics
Reflux
Non – human
Gestational diabetes
Catheters
Neonatal urinary tract infection
Paediatric urinary tract infection
Post menopausal
Transplant

4.2 Key citation selection

The 71 citations identified in the initial search were triaged into those:

- Possibly containing relevant evidence or authoritative opinion (29 citations), and
- Unlikely to contain relevant evidence or authoritative opinion (42 citations). These citations were either too general or not relevant to the topics to be addressed and were not considered further.

The 29 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 14 articles were classified as key citations, and were subjected to systematic critical appraisal by the project team (Appendix IV) and those not meeting the criteria were discarded.

The evidence within these 14 key citations fell into the following levels (see Appendix IV for definitions):

Level I evidence: 2 publications (one included in the original literature review)

Level II evidence: 0 publications,

Level III evidence: 8 publications, and

Level IV evidence: 4 publications.

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.

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- 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.

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

Asymptomatic bacteriuria (ASB) is the persistent bacterial colonisation of the urinary tract without urinary tract symptoms. Studies conducted in the USA state the incidence of ASB is between two and ten percent, higher among women of lower socio-economic status. In the United Kingdom, studies report **incidence between two and five percent of pregnant women**¹.

5.1 Does routine screening for asymptomatic bacteriuria during pregnancy (and treatment of those found to be positive) result in improved outcomes (less urinary tract infections, preterm birth and low birth weight) compared with no screening?

Urinary tract infections

- **Reference**

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003.

In the review of the evidence to 2003, RCOG conclude the randomized controlled trials (RCTs) conducted to demonstrate the benefit of treatment for women with ASB also indicate an increased risk between ASB and maternal and fetal outcomes, such as preterm birth and pyelonephritis, among untreated women compared with women without bacteriuria. The reported increased risk of pyelonephritis among pregnant women with ASB ranges from a risk difference of 1.8% to 28%¹.

- **Reference**

United States Preventive Services Task Force (USPSTF) Screening for asymptomatic bacteriuria: recommendation statement Rockville (MD): *Agency for Healthcare Research and Quality (AHRQ)* 2004.

USPSTF strongly recommend screening of all pregnant women at 12-16 weeks' gestation for ASB using urine culture. According to USPSTF, screening at 12-16 weeks' gestation will detect approximately 80 percent of patients with ASB².

These two evidence based guidelines refer to Cochrane Reviews related to ASB in pregnancy:

- Following examination of 14 RCTs conclusions (consistent with the earlier Cochrane Review), that antibiotic treatment of ASB appeared to reduce the risk of pyelonephritis in pregnancy with an apparent reduction in preterm delivery. Antibiotic treatment reduced persistent bacteriuria during pregnancy (Peto OR 0.07, 95% CI 0.05 to 0.10), reduced risk of preterm delivery or low-birthweight babies (OR 0.60, 95% CI 0.45 to 0.80), and reduced risk of development of pyelonephritis (OR 0.24, 95% CI 0.19 to 0.32, NNT7)³.
- Comparison of single-dose antibiotic treatment with a 4 to 7 day course of antibiotic treatment for ASB showed no difference in the prevention of preterm birth (RR 0.81, 95% CI 0.26 to 2.57) or pyelonephritis (RR 3.09, 95% CI 0.54 to 17.55). Longer duration of treatment, however, was associated with increased reports of adverse effects (RR 0.53, 95% CI 0.31 to 9.91)⁴.

Project team comment

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The new evidence strengthens the previously reported associations of ASB and pyelonephritis, preterm birth and low birth weight. The concerns of adverse events related to longer duration of treatment require closer examination.

- **Reference**

Puil L, Mail J, Wright JM. Asymptomatic bacteriuria during pregnancy. Rapid answers using the Cochrane Library. *Canadian Family Physician*;48:58-60. (Level IV)

In a review of the five Cochrane Reviews for related to ASB in pregnancy, this study uses case presentations to evaluate the available evidence. It found that ~6% of pregnant women screened have ASB. Given a 14.6% absolute risk reduction (ARR) with an antibiotic, 114 women ($1/[0.06 \cdot 0.146]$) would have to be screened to prevent one case of pyelonephritis⁵.

Project team comment

This paper examines Level I evidence and applies conclusions in a practical presentation.

Preterm birth

- **Reference**

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003

RCOG guidelines conclude women who have untreated ASB have an increased risk of preterm birth compared with women who do not have ASB. There is a large risk difference (from 2.1% to 12.8%) possibly due to variation in effect size over time because earlier studies reported larger effects than more recent studies. In addition, many of the earlier studies did not specify the method of randomization, or were open to bias because of quasi-random allocation to treatment versus control groups.

- **Reference**

Hill JB, Sheffield JS, McIntire DD, Wendel GD, Jr. Acute pyelonephritis in pregnancy. *Obstetrics & Gynecology* 2005;105(1):18-23.

A longitudinal study involving 440 cases of acute antenatal pyelonephritis identified during the study period an incidence of acute pyelonephritis in pregnancy of 1.4%. The incidence of pyelonephritis has remained low in the era of routine prenatal screening for ASB. Maternal complications continue, but poor obstetrical outcomes are rare⁶.

The reported incidence of preterm births and small-for-gestational-age infants in this study were not increased compared with previously reported results possibly because of improvements in acute care, as well as aggressive follow-up care and antimicrobial urinary suppression.

53% of events occurred in the second trimester, and this study noted more first trimester cases and fewer third trimester cases than found in historical reports. The study investigated the unexpected increased frequency of acute pyelonephritis in the first trimester. An examination of the common maternal risk factors found only diabetes as more common in the first trimester cases.

Among women with positive urine cultures, 83% identified E coli. This is similar to that reported in 1981. This study found a preponderance of infection with E coli, fewer cases from the Klebsiella-Enterobacter group, and more cases caused by gram-positive organisms, predominantly group B Streptococcus and other gram-positive organisms, accounting for nearly 1 in 8 hospitalized cases of acute pyelonephritis with positive urine cultures.

Project team comment

Complete birth data were only available for 368 women and their infants, raising some concerns regarding the validity of the results. However, the described shift in the microbiologic pattern of infection has clinical implications, especially in the third trimester; when antimicrobial treatment is chosen empirically based on a presumption of urine culture results and issues surround the presence of Group B Streptococcus.

Project team overall conclusion

The incidence of ASB in pregnancy is 6%. Untreated in pregnancy, ASB risks include pyelonephritis (20%) and preterm birth (10%). Compared with no screening, routine screening for ASB in pregnancy appears to result in improved outcomes of 40% reduced risk of preterm delivery or low-birthweight babies, and 80% reduced risk of development of pyelonephritis. Long-term outcomes have not been thoroughly investigated. This evidence is primarily drawn from existing guidelines. More recent evidence raises concerns regarding the number needed to treat where there is improved perinatal care. Additional concerns are that treatment may be altering the profile of microbiosis.

Recommendation (A)

The routine screening for ASB during pregnancy and treatment of those found to be positive is recommended to improve outcomes with respect to less urinary tract infections, preterm birth and low birth weight.

5.2 In pregnant women, which method is more accurate at detecting asymptomatic bacteriuria – dipstick reagent testing or laboratory culturing of a voided MSU specimen?

• Reference

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003.

RCOG guidelines state “urine culture (midstream) has been used as the reference standard for diagnosis of ASB. In studies of ASB, a growth of 10⁵ organisms of a single uropathogen per millilitre in a single midstream sample of urine is considered significant, although some tests have used figures such as 10⁴ and 10⁸. When urine culture is used in screening for ASB, the drawbacks include the time lag: results are not usually available for at least 24 hours, and the cost: £1.40 in a 1993 UK study compared with the maximum cost of a reagent strip test of £0.14. Its advantages are in being able to identify causative organisms and determine antibiotic sensitivities”^{1:79}.

In examination of evidence regarding sensitivity and specificity for reagent strip testing, RCOG state “At best, reagent strip testing will detect 50% of women with ASB”^{1:80}.

“Other tests identified include the urinary interleukin-8 test and the rapid enzymatic test, both of which have a sensitivity of 70% and will potentially miss 30% of women with ASB. A bioluminescence test has been described, with a sensitivity of 93% and a specificity of 78%”^{1:80}.

• Reference

United States Preventive Services Task Force (USPSTF) Screening for asymptomatic bacteriuria: recommendation statement Rockville (MD): *Agency for Healthcare Research and Quality (AHRQ)* 2004.

USPSTF do not recommend using leukocyte esterase or nitrite testing for routine screening of pregnant women because of poor test characteristics compared with urine culture².

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- **Reference**

Deville WL, Yzermans JC, van Duijn NP, Bezemer PD, van der Windt DA, Bouter LM. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urology* 2004;4(1):4.

A meta-analysis of 70 publications in the general population concludes that in pregnant women, a negative dipstick test (nitrites or leukocyte-esterase) rules out infection (specificity 85-98%) whilst a positive nitrite test still requires workup, although the probability of infection increases considerably and sensitivities of the combined test are reported as 68-88%⁷.

Project team comment

This was a well conducted meta-analysis involving studies published from 1990 to 1999. Only ten studies were specific to pregnancy. The accuracy of nitrites was reported as high in pregnant women. Conclusions support the use of dipstick as a screening tool for urinary tract infection or bacteriuria.

- **Reference**

Teppa RJ, Roberts JM. The uriscreen test to detect significant asymptomatic bacteriuria during pregnancy. *Journal of the Society for Gynecologic Investigation* 2005;12(1):50-3.

A prospective cohort study investigated the Uristix (enzymatic) testing for ASB. Sensitivity, specificity, and positive and negative predictive values for the Uriscreen test were 60.7% (+/-18.1), 89.3% (+/-5.6), 56.6%, and 90.8%, respectively⁸.

Project team comment

The methodology described appeared cumbersome and power calculations were not delineated. The findings do not support Uristix as a screening tool for ASB due to the inadequate sensitivity.

- **Reference**

Tamayo J, Gomez-Garces JL, Alos JI. Evaluation of Granada agar plate for detection of *Streptococcus agalactiae* in urine specimens from pregnant women. *Journal of Clinical Microbiology* 2004;42(8):3834-6.

A prospective cohort, laboratory based study found the Granada agar plate detected 103/105 cases of GBS, whilst the blood agar plate only detected 50/105. The study concluded that GAP medium may be more suitable for detection of GBS in pregnant women tested for ASB⁹.

Project team comment

The objective of this study was to evaluate the Granada agar plate for the detection of GBS in urine specimens of pregnant women compared with the existing method using blood agar plates for culture. The improved detection rate of GBS is an important finding following the findings reported by Hill et al on the changing profile of infective organisms in pyelonephritis in pregnancy.

- **Reference**

D'Souza Z, D'Souza D. Urinary tract infection during pregnancy--dipstick urinalysis vs. culture and sensitivity. *Journal of Obstetrics & Gynaecology* 2004;24(1):22-4.

The purpose of this cohort study was to determine whether using the Nephur Labsticks for urinalysis was an accurate tool for diagnosing a UTI in pregnant women admitted with symptoms suggestive of UTI. When compared with culture and sensitivity in the microbiology laboratory, the negative tests on dipstick were negative

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on C&S. However, the authors recommended treatment with antibiotics and confirmatory C&S if strongly positive for nitrites based on 2 out of 2 such examples culturing E coli. In this study the 45 cases with leukocytes, blood and protein detected by dipstick resulted in a negative C&S¹⁰.

Project team comment

This was a small study in the setting of women symptomatic for UTI, therefore the external validity is uncertain. Nevertheless, it supports the use of dipstick as a screening tool with confirmatory C&S testing if dipstick is positive for nitrites.

• Reference

Kutlay S, Kutlay B, Karaahmetoglu O, Ak C, Erkaya S. Prevalence, detection and treatment of asymptomatic bacteriuria in a Turkish obstetric population. *Journal of Reproductive Medicine* 2003;48(8):627-30.

This cohort study evaluated the results of midstream urine sample of 406 pregnant women. The prevalence of ASB (n = 43) was 10.6%, and symptomatic UTI (n = 19) was 4.7%. The sensitivity and specificity of microscopic urinalysis were 71.0% and 73.6% respectively. The sensitivity and specificity of the dipstick testing were 38.7% and 35.8%, respectively¹¹.

Project team comment

Although there is limited power to this study, it supports findings of other studies examined for this topic. There is limited demographic data to assess the applicability to the Australian population.

Project team overall conclusion

Culture of voided MSU specimen remains the gold standard for detecting ASB in pregnancy. The drawbacks of urine culture include delay in result availability and cost. Advantages include being able to identify causative organisms and ability to determine antibiotic sensitivities.

Reagent strip testing will detect 50% of women with ASB, and uriscreen (enzymatic test) will detect 60%. The specificity of reagent strip testing of 90% is reassuring in that only 10% of women without ASB will require confirmatory testing with urine culture of a MSU specimen.

Therefore evidence suggests that dipstick testing is a reasonable method of exclusion of ASB as the specificity and negative predictive value in low risk women appears to be in excess of 90%. However, culture remains the gold standard, and should definitely be performed if dipstick testing is positive.

Recommendation (B-C)

Laboratory culturing of a voided MSU specimen is more accurate at detecting ASB in pregnant women.

However, this recommendation should consider the cost and time which may make dipstick reagent testing or enzymatic testing more attractive options for routine screening for ASB in pregnancy.

5.3 Is it more cost effective to screen women for asymptomatic bacteriuria using dipstick reagent testing or laboratory culturing of a voided MSU specimen?

• Reference

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003.

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The RCOG guidelines state that antenatal screening for ASB can have important healthcare resource consequences associated with the reduction of maternal and infant morbidity particularly in relation to preterm birth and the consequent lifetime costs of disability associated with preterm birth. That is, compared with no screening both dipstick and urine culture are cost effective strategies¹.

In the assessment of the evidence for comparative cost effectiveness, analysis supported the conclusion that the culture method is favourable, use of dipstick method over culture resulted in further costs of £32,400 per additional preterm birth prevented¹.

Further to this the guidelines refer to a threshold analysis which explored the circumstances under which the screening options would have similar costs. Results indicated that for the two screening strategies to have equal overall costs (including the cost of preterm birth), the sensitivity of the dipstick method would have to be equal to or greater than 0.912. As this is not achieved in any study, the culture method is more cost effective in comparison to the dipstick method¹.

• Reference

Hundley AF, Onderdonk AB, Greenberg JA. Value of routine urine culture in the assessment of preterm labor. *Journal of Reproductive Medicine* 2003;48(11):853-7.

A retrospective cohort study evaluated more than 500 urine cultures in the setting of evaluation for preterm labour. Six reported growth >100,000 colonies of a single bacteria. Only one of the six was asymptomatic. Overall cost of investigation was just under \$60 per woman¹².

The study reported no clinical significance of urine culture as a predictor of preterm birth (sensitivity 0.7%, specificity 98.6% and positive predictive value 16.7%) in the setting of evaluation for preterm labour. It is important to note that only one patient with ASB was evaluated for preterm labour and cervical incompetence was thought to be the aetiology of her preterm delivery¹².

The authors conclude that routine urinary culture in the setting of assessment for preterm labour is not cost effective unless specific urinary symptoms are to be investigated based on the lack of sensitivity of the test¹².

Project team comment

This was the only additional citation identified relevant to this topic.

There are methodological concerns regarding the consistency of assessing preterm labour and the lack of uniformity that this poses. The study does not specifically address the question of whether ASB screening is cost effective or whether dipstick screening is more cost effective than culture.

Project team overall conclusion

It is more cost effective to screen women for ASB, with respect to prevention of preterm delivery, by midstream urine specimen culture. Laboratory culture appears to be more cost effective than dipstick reagent testing due to the poor sensitivity of the dipstick reagent testing of 50%.

However, in the clinical setting of evaluation of signs and symptoms of preterm labour, urinary culture appears to be a poor predictor of subsequent preterm delivery.

Recommendation (C)

It is more cost effective to screen women for ASB with respect to prevention of preterm delivery using laboratory culture rather than dipstick reagent testing.

5.4 Is it more effective to screen for asymptomatic bacteriuria (by the most effective detection method) at booking or only in later pregnancy (after 26 weeks) in terms of urinary tract infections, preterm birth and low birth weight?

- **Reference**

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003.

The RCOG recommend that routine screening for ASB by midstream urine culture should be offered to pregnant women early in pregnancy, as the identification and treatment of ASB reduces the risk of preterm birth¹.

Project team comment

This recommendation appears to be based on evaluation of previous evidence in which ASB screening was performed early in pregnancy. The specific question of testing early or later in pregnancy does not appear to have been addressed in this guideline.

- **Reference**

United States Preventive Services Task Force (USPSTF) Screening for asymptomatic bacteriuria: recommendation statement Rockville (MD): *Agency for Healthcare Research and Quality (AHRQ)* 2004.

The USPSTF “strongly recommends” screening for ASB using urine culture for all pregnant women at 12-16 weeks’ gestation. The guideline reports that a specimen obtained at 12-16 weeks gestation will detect approximately 80% of women with ASB².

They further comment that the optimal frequency of subsequent urine testing during pregnancy is uncertain².

Project team comment

The USPSTF grade this recommendation as ‘level A’, however the reported evidence is very limited.

- **Reference**

Hill JB, Sheffield JS, McIntire DD, Wendel GD, Jr. Acute pyelonephritis in pregnancy. *Obstetrics & Gynecology* 2005;105(1):18-23.

A prospective cohort study found that 79% of cases of acute pyelonephritis occurred in the last 2 trimesters of pregnancy, but more than 1 in 5 cases occurred in the first trimester. Findings support screening for ASB in the 1st trimester⁶.

Project team comment

Whilst not directly addressing the topic, the small incidence of acute pyelonephritis and in particular the 20% proportion in the first trimester, adds weight to testing at the first antenatal visit.

- **Reference**

Mclsaac W, Carroll JC, Biringir A et al. Screening for asymptomatic bacteriuria in pregnancy. *Journal of Obstetrics Gynaecology Canada* 2005; 27(1):20-24.

A large prospective cohort study evaluated 1050 women prospectively with urinary cultures and leukocyte-esterase-nitrite (LEN) strips at booking and each trimester¹³.

They found that a single urine culture before 20 weeks gestation missed more than half ASB cases. A culture in each trimester had the greatest detection rate of ASB of

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(43/49 cases ASB, 87.8%). Single culture detected 20/49 cases (40.8%) and dipstick testing detected 7/49 cases (14.3%)¹³.

Project team comment

The methodology of this study is of sufficient quality regarding internal and external validity. Findings support the use of urinary culture over dipstick testing but raise issues of repeat testing in pregnancy, with concomitant cost considerations.

• Reference

O'Neill MS, Hertz-Picciotto I, Pastore LM, Weatherley BD. Have studies of urinary tract infection and preterm delivery used the most appropriate methods? *Paediatric and Perinatal Epidemiology* 2003;17(3):226-33.

A retrospective cohort study examined the application of logistic regression or chi-squared tests when researchers have investigated the association between UTI and preterm birth. As both exposure and outcome are time dependent, these methods were considered suboptimal and did not account for person-time under observation (which is an important feature given the variability of women's entry to prenatal care and length of gestation). Previous investigations probably classified as exposed some women whose UTI occurred after their pregnancies exceeded 37 weeks gestation. Two logistic regression models were fitted with differing exposure definitions, with and without five time-constant potential confounders¹⁴.

The authors concluded that previous published results on UTI and preterm birth require cautious interpretation. They recommend collection of data on UTI timing to allow appropriate analyses; survival methods account for person-time under observation and ensure that studied exposures precede effects¹⁴.

Project team comment

The authors have completed a complex analysis of statistical models comparing hazard ratio with odds ratio taking into account exposure over time. Their findings exhort us to interpret current evidence with caution.

Project team overall conclusion

Guidelines continue to recommend screening for ASB at 12-16 weeks gestation based on historical evidence. The evidence for this is not explicit. The only relevant new citation identified by the project team found that testing prior to 20 weeks gestation missed over half ASB cases and recommended a culture in each trimester for the greatest detection of ASB. The detection rate for ASB is improved 2-fold with testing each trimester.

This raises issues related to cost, which have not been specifically evaluated in the literature.

Recommendation (C)

The project team agrees with the existing guidelines which continue to recommend screening at 12-16 weeks gestation.

6. Conclusions and recommendations

6.1 Does routine screening for asymptomatic bacteriuria during pregnancy (and treatment of those found to be positive) result in improved outcomes (less urinary tract infections, preterm birth and low birth weight) compared with no screening?

The incidence of ASB in pregnancy is 6%. Untreated in pregnancy, ASB risks include pyelonephritis (20%) and preterm birth (10%). Compared with no screening, routine screening for ASB in pregnancy appears to result in improved outcomes of 40%

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reduced risk of preterm delivery or low-birthweight babies, and 80% reduced risk of development of pyelonephritis. Long-term outcomes have not been thoroughly investigated. This evidence is primarily drawn from existing guidelines. More recent evidence raises concerns regarding the number needed to treat where there is improved perinatal care. Additional concerns are that treatment may be altering the profile of microbiosis.

Recommendation (A)

The routine screening for ASB during pregnancy and treatment of those found to be positive is recommended to improve outcomes with respect to less urinary tract infections, preterm birth and low birth weight.

6.2 In pregnant women, which method is more accurate at detecting asymptomatic bacteriuria – dipstick reagent testing or laboratory culturing of a voided MSU specimen?

Culture of voided MSU specimen remains the gold standard for detecting ASB in pregnancy. The drawbacks of urine culture include delay in result availability and cost. Advantages include being able to identify causative organisms and ability to determine antibiotic sensitivities.

Reagent strip testing will detect 50% of women with ASB, and uriscreen (enzymatic test) will detect 60%. The specificity of reagent strip testing of 90% is reassuring in that only 10% of women without ASB will require confirmatory testing with urine culture of a MSU specimen.

Therefore evidence suggests that dipstick testing is a reasonable method of exclusion of ASB as the specificity and negative predictive value in low risk women appears to be in excess of 90%. However, culture remains the gold standard, and should definitely be performed if dipstick testing is positive.

Recommendation (B-C)

Laboratory culturing of a voided MSU specimen is more accurate at detecting ASB in pregnant women.

However, this recommendation should consider the cost and time which may make dipstick reagent testing or enzymatic testing more attractive options for routine screening for ASB in pregnancy.

6.3 Is it more cost effective to screen women for asymptomatic bacteriuria using dipstick reagent testing or laboratory culturing of a voided MSU specimen?

It is more cost effective to screen women for ASB, with respect to prevention of preterm delivery, by midstream urine specimen culture. Laboratory culture appears to be more cost effective than dipstick reagent testing due to the poor sensitivity of the dipstick reagent testing of 50%.

However, in the clinical setting of evaluation of signs and symptoms of preterm labour, urinary culture appears to be a poor predictor of subsequent preterm delivery.

Recommendation (C)

It is more cost effective to screen women for ASB with respect to prevention of preterm delivery using laboratory culture rather than dipstick reagent testing.

6.4 Is it more effective to screen for asymptomatic bacteriuria (by the most effective detection method) at booking or only in later pregnancy (after 26 weeks) in terms of urinary tract infections, preterm birth and low birth weight?

Guidelines continue to recommend screening for ASB at 12-16 weeks gestation based on historical evidence. The evidence for this is not explicit. The only relevant

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new citation identified by the project team found that testing prior to 20 weeks gestation missed over half ASB cases and recommended a culture in each trimester for the greatest detection of ASB. The detection rate for ASB is improved 2-fold with testing each trimester.

This raises issues related to cost, which have not been specifically evaluated in the literature.

Recommendation (C)

The project team agrees with the existing guidelines which continue to recommend screening at 12-16 weeks gestation.

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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	Routine screening for asymptomatic bacteriuria
C	No screening
O	Urinary tract infections Preterm birth Low birth weight Detection of asymptomatic bacteriuria Cost effectiveness

Search findings

Term	Medline	Premedline	CINAHL	EBM
Asymptomatic bacteriuria / bacteriuria / urinary tract infections / pyelonephritis + pregnan\$ / pregnancy / prenatal diagnosis / prenatal care / antenatal	96/323	3/4	7/48	0/2
Urinalysis / urine test / dipstick / reagent strips / sensitivity & specificity / reagent kits diagnostic / MSU / culture & urine + asymptomatic bacteriuria / bacteriuria / urinary tract infections + pregnan\$ / pregnancy / prenatal diagnosis / prenatal care / antenatal	20/33			
Urinalysis / urine test / dipstick / reagent strips / sensitivity & specificity / reagent kits diagnostic / MSU / culture & urine + pregnan\$ / pregnancy / prenatal diagnosis / prenatal care / antenatal		0/2	18/313	0/2
Urinalysis / urine test / dipstick / reagent strips / sensitivity & specificity / reagent kits diagnostic / MSU / culture & urine + cost effective / cost benefit analysis	3/7			
Urinalysis / urine test / dipstick / reagent strips / sensitivity & specificity / reagent kits diagnostic / MSU / culture & urine + screen\$	/461		5/255	

Cochrane

	Systematic Review	DARE	Central Register
Asymptomatic bacteriuria	2/28	0/5	2/13
Midstream urine / urinalysis	*2/12	/0	0/8
Urinary tract infection + pregnancy / antenatal / prenatal	*2/85	0/1	0/14
Urinalysis / urine test + pregnancy / antenatal / prenatal	0/66	0/9	*2/1778

Literature Search and Appraisal

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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9. Tamayo J, Gomez-Garces JL, Alos JI. Evaluation of Granada agar plate for detection of *Streptococcus agalactiae* in urine specimens from pregnant women. *Journal of Clinical Microbiology* 2004;42(8):3834-6. (Level III-2)
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2.1 Does routine screening for asymptomatic bacteriuria during pregnancy (and treatment of those found to be positive) result in improved outcomes (less urinary tract infections, preterm birth and low birth weight) compared with no screening?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Smaill F 2001	3	14 RCTs that compared antibiotic treatment with placebo or no treatment in pregnant women with ASB found on antenatal screening.	Antibiotic treatment	Effect of antibiotic treatment for ASB on: <ul style="list-style-type: none"> Persistent bacteriuria during pregnancy Risk of preterm birth Development of pyelonephritis 	<ul style="list-style-type: none"> Antibiotic treatment compared to placebo or no treatment was effective in clearing ASB (OR 0.07, 95% CI 0.05-0.10) The incidence of pyelonephritis was reduced (OR 0.24, 95% CI 0.19-0.32) Antibiotic treatment was associated with a reduction in the incidence of preterm birth or low birth weight babies (OR 0.60, 95% CI 0.45-0.80) 	Systematic review	I
Hill JB, Sheffield JS et al 2005	6	Parkland Hospital, Dallas, Texas United States January 2000 – December 2001 All pregnant women admitted with acute pyelonephritis 440 cases, complete data available for 368 women and infants	Hospitalization, intravenous antibiotics.	Pregnancy outcomes	<p>Incidence of acute antenatal pyelonephritis = 1.4%.</p> <p>Pyelonephritis was associated with nulliparity (44% versus 37%, $P=.003$) and young age ($P=.003$).</p> <p>79% of cases of pyelonephritis occurred during the last two trimesters. The majority of cases occurred in the second trimester (53%).</p> <p>Most common risk factor was previous history of pyelonephritis and ASB.</p> <p>Of the 368 women:</p> <ul style="list-style-type: none"> 19 (5%, 95% CI 13-8%) delivered a preterm infant <37 weeks gestation. 6 of these were <32 weeks. 26 women (7%, 95% CI 5-10%) delivered infant <2500 gm. 12 women (2.7%, 95% CI 1.4-4.7%) were readmitted for recurrent pyelonephritis. 1 in 8 hospitalised cases had predominantly group B Streptococcus and other gram-positive organisms. In the third trimester, 1 in 4 cases of pyelonephritis was due to an organism other than E coli. <p>Numbers of preterm births and small-for-gestational age infants were not increased compared with expected rates. Previous increased rates of adverse pregnancy outcomes were not observed.</p>	Cohort study	III-2

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2.2 In pregnant women, which method is more accurate at detecting asymptomatic bacteriuria – dipstick reagent testing or laboratory culturing of a voided MSU specimen?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Teppa RJ, Roberts JM 2005	7	Dr Dominigo Luciani Hospital, Caracas, Venezuela May 2003 150 women who had routine prenatal screening for ASB	Catheterised urine samples	Reliability of an enzymatic urine screening test (Uriscreen) for detecting asymptomatic bacteriuria in pregnancy	<ul style="list-style-type: none"> Sensitivity, specificity, and the positive and negative predictive values for the Uriscreen were estimated using urine culture as the criterion standard. Urine cultures were considered positive if they grew >10(5) colony-forming units of a single uropathogen. 28 women (18.7%) had urine culture results indicating significant bacteriuria. 17 of these had positive enzyme activity. Those 122 samples with no growth included 109 with negative enzyme activity. Sensitivity, specificity, and positive and negative predictive values for the Uriscreen test were 60.7% (+/-18.1), 89.3% (+/-5.6), 56.6%, and 90.8%, respectively. <p>Authors concluded that “the Uriscreen test had inadequate sensitivity for rapid screening of bacteriuria in pregnancy”.</p>	Cohort study	III-2
Tamayo J, Gomes-Garces JL et al 2004	9	Hospital de Mostoles, Madrid, Spain 834 urine specimens of pregnant women January – August 2003	Granada agar plate (GAP) and blood agar (BA)	Detection of GBS in urine Manageability Costs	<p>Detection</p> <ul style="list-style-type: none"> GBS was detected with one of the 2 media in 105 of the 834 urine specimens cultured. GAP detected 103 of the 105 BA detected 50 of the 105. <p>Manageability</p> <ul style="list-style-type: none"> GAP enables easy visual identification, no specialized personnel required for identification GAP has short shelf life <p>Costs</p> <ul style="list-style-type: none"> GPA is more expensive than BA (\$2.54 versus \$0.74 per unit). However, one GAP can be used for 4 urine specimens. 	Cohort study	III-2
Deville W, Yzermans JC et al	7		Dipstick test for nitrites and/or leukocyte esterase.	Accuracy as rapid detectors of bacteriuria and UTI.	<ul style="list-style-type: none"> 70 publications were included. Accuracy of: <ul style="list-style-type: none"> Nitrites was high in pregnant women (diagnostic OR=165). Leukocyte-esterase was high in studies in urology patients (diagnostic OR = 276). Sensitivities were highest in family medicine (86%). Negative predictive values were high in both tests in all patient groups and settings, except family medicine. Combining both test results increased sensitivity. Accuracy was high in studies in urology patients (DOR = 52), in 	Meta analysis	IV

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children (DOR = 46).

- Predictive values of combinations of positive test results were low in all other situations.

Authors conclude that the urine dipstick test alone seems to be useful in all populations to exclude the presence of infection if the results of both nitrites and leukocyte-esterase are negative. Positive test results should be confirmed.

D'Souza Z and D'Souza D 2004	10	Birmingham Women's Hospital, United Kingdom January – March 2002 Pregnant women who attended the birth suite with symptoms suggestive of urinary tract infections	Urinary dipsticks (Nephrur Labsticks - Roche Diagnostics)	Diagnosing urinary tract infection	<ul style="list-style-type: none"> • 100 samples collected, tested and sent for culture and sensitivity (C&S) testing. • 53 samples which had no abnormalities detected on dipstick, nothing was found on C&S testing. • 2 samples had strong positive result for nitrites (and white blood cells, blood and protein) and the culture result showed E Coli in both samples. <p>Authors recommend:</p> <ul style="list-style-type: none"> • If MSU tested by dipstick as negative, there is no need for C&S • If leucocytes, blood or protein are found the sample needs to be sent to the laboratory, but withhold antibiotics until C&S results available • If nitrites are found the sample must be sent to the laboratory but antibiotic treatment may be indicated before C&S results are available. 	Prospective cohort study	III-2
Kutlay S, Kutlay B et al 2003	11	Zubeyde Harum Maternity Hospital, Ankara, Turkey September – December 2000 412 pregnant women admitted for initial obstetric examination during the first trimester.	Clean catch urine culture, microscopic urinalysis and dipstick urine tests	Sensitivity and specificity of each intervention	<ul style="list-style-type: none"> • Prevalence of ASB (n = 43) was 10.6%, and symptomatic UTI (n = 19) was 4.7%. • The sensitivity and specificity of: <ul style="list-style-type: none"> ○ Microscopic urinalysis were 71.0% and 73.6% respectively ○ Dipstick testing were 38.7% and 35.8%, respectively. • 83% of ASB/UTI cases were effectively treated with a course of a single antimicrobial (amoxicillin or a first-generation cephalosporin). <p>Authors conclude that "if untreated, ASB can lead to acute, symptomatic UTI, including acute pyelonephritis, which in turn is associated with preterm labor and low birth weight. Therefore, screening for ASB early in pregnancy by methods with high sensitivity and treatment with appropriate antimicrobial regimens can decrease the risk of symptomatic UTI. In a Turkish clinical unit where culture is not available, the use of microscopic urinalysis was a clinically effective alternative method of detecting ASB. In this study, the sensitivity and specificity of dipstick testing were not high enough to recommend them as means of detecting ASB/UTI.</p>	Cohort study	III-2

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2.3 Is it more cost effective to screen women for asymptomatic bacteriuria using dipstick reagent testing or laboratory culturing of a voided MSU specimen?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Hundley AF, Onderdonk AB et al 2003	12	Brigham & Women's Hospital, Boston, United States 1 January – 31 December 2000 1429 women admitted to the birth suite with diagnosis indicating evaluation of preterm labour	Urine culture		<ul style="list-style-type: none"> • 512 had urine cultures undertaken: • 6 (1.2%) reported growth of > 100,000 colonies of a single bacterium. • Of these 6 patients, 5 reported symptoms consistent with a urinary tract infection, while the 6th was asymptomatic. • There was no clinical significance for a positive urine culture as a predictor of preterm delivery (P = .68). • Sensitivity was 0.7% (95% CI, 0.0-4.3), and specificity was 98.6% (95% CI, 96.7-99.5). • A cost difference of \$29,676 existed between charges and reimbursements. This cost analysis for the hospital assumed 100% sensitivity and specificity for urine culture and was based on the difference between total charges incurred and total reimbursements. <ul style="list-style-type: none"> ○ Laboratory charge for single urine culture @ \$68 ○ Laboratory charge for sensitivity testing @ \$82 ○ Insurance reimbursement @ \$11.16 • A positive culture was not a significant risk factor for preterm delivery. <p>Authors conclude: "The routine use of urine cultures in the assessment of preterm labor is costly and adds little value to obtaining a diagnosis except in the presence of specific complaints at our institution. Urine culture identified a single patient with ASB being evaluated for preterm labor, and she probably had another etiology for her advanced cervical examination."</p>	Retrospective cohort study	III-2

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2.4 Is it more effective to screen for asymptomatic bacteriuria (by the most effective detection method) at booking or only in later pregnancy (after 26 weeks) in terms of urinary tract infections, preterm birth and low birth weight?

Study	Ref.	Population	Interventions	Outcomes	Results	Study type	EL
Mclsacc W, Carroll JC et al 2005	13	Mount Sinai Hospital, Toronto Canada/ 1050 women attending antenatal clinic July 1996 – April 1998	Leukocyte-esterase nitrite (LEN) strips at each antenatal visit followed by a urine culture if positive, A single urine culture at \leq 20 weeks gestation A single urine culture at \leq 20 weeks gestation and at 28 weeks gestation or 3 urine cultures at \leq 20 weeks, 28 weeks and 36 weeks gestation.	Detection of ASB	<ul style="list-style-type: none"> • A single urine culture before 20 weeks gestation missed more than half ASB cases. • A culture in each trimester had the greatest detection rate of ASB of (43/49 cases ASB, 87.8%). • Single culture detected 20/49 cases (40.8%) and dipstick testing detected 7/49 cases (14.3%) 	Cohort study	III-2