


BMJ Open Diagnostic work-up of urinary tract infections in pregnancy: study protocol of a prospective cohort study

Dominique Esmée Werter ,¹ Brenda M Kazemier,¹ Elisabeth van Leeuwen,² Maurits C F J de Rotte,³ Sacha D Kuil,⁴ Eva Pajkrt,⁵ Caroline Schneeberger^{6,7}

To cite: Werter DE, Kazemier BM, van Leeuwen E, *et al.* Diagnostic work-up of urinary tract infections in pregnancy: study protocol of a prospective cohort study. *BMJ Open* 2022;**12**:e063813. doi:10.1136/bmjopen-2022-063813

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-063813>).

Received 12 April 2022
Accepted 30 August 2022

ABSTRACT

Introduction Symptoms of urinary tract infections in pregnant women are often less specific, in contrast to non-pregnant women where typical clinical symptoms of a urinary tract infection are sufficient to diagnose urinary tract infections. Moreover, symptoms of a urinary tract infection can mimic pregnancy-related symptoms, or symptoms of a threatened preterm birth, such as contractions. In order to diagnose or rule out a urinary tract infection, additional diagnostic testing is required. The diagnostic accuracy of urine dipstick analysis and urine sediment in the diagnosis of urinary tract infections in pregnant women has not been ascertained nor validated.

Methods and analysis In this single-centre prospective cohort study, pregnant women (≥ 16 years old) with a suspected urinary tract infection will be included. The women will be asked to complete a short questionnaire regarding complaints, risk factors for urinary tract infections and baseline characteristics. Their urine will be tested with a urine dipstick, urine sediment and urine culture. The different sensitivities and specificities per test will be assessed. Our aim is to evaluate and compare the diagnostic accuracy of urine dipstick analysis and urine sediment in comparison with urine culture (reference test) in pregnant women. In addition, we will compare these tests to a predefined 'true urinary tract infection', to distinguish between a urinary tract infection and asymptomatic bacteriuria.

Ethics and dissemination Approval was requested from the Medical Ethics Review Committee of the Academic Medical Centre; an official approval of this study by the committee was not required. The outcomes of this study will be published in a peer-reviewed journal.

INTRODUCTION

The prevalence of urinary tract infections (UTIs) during pregnancy reported in literature varies between 2.3% and 15%.^{1–5} It is hypothesised that anatomical changes during pregnancy such as dilatation of the ureters, decreased ureteral tone and increased bladder volume contribute to urinary stasis and ureterovesical reflux increasing the risk of a UTI.^{6–8} Besides the anatomical changes, pregnancy-related glomerular filtration rate increases the alkalinity of the urine and the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The urine of every participating woman will be tested with a set of tests including a urine dipstick, urine sediment and a urine culture.
- ⇒ We will investigate the course of complaints in pregnant women with a possible urinary tract infection to gain more insight in the diagnostic value.
- ⇒ The research will be done prospectively; therefore, we expect less bias than in a retrospective cohort.
- ⇒ It will be a single-centre cohort study, so it could possibly make the participants more homogeneous.

urinary glucose concentration, which facilitates bacterial growth.⁹ The association between UTIs during pregnancy and maternal complications such as hypertensive disorders and caesarean delivery has been reported, although there is contradictory evidence.^{4 6 10} Moreover, UTIs during pregnancy have also been associated with neonatal complications such as preterm birth, low birth weight and perinatal death.^{2 4 10} In addition, an untreated UTI may lead to pyelonephritis, which further increases the risk of preterm birth.¹¹ Preterm birth has major consequences at the individual level as well as for society (costs).

In contrast, overtreating pregnant women with antibiotics may also cause harm. Overuse and incorrect use of antibiotics are the main causes of antimicrobial resistance. Moreover, the unnecessary exposure of the unborn child to antibiotics may also not be without risks. Associations between antibiotics during pregnancy and adverse neonatal outcomes including increased risk of cerebral palsy, early-onset sepsis with antibiotic-resistant microorganisms, malformations and epilepsy have been published.^{10 12 13} Also, maternal exposure to certain antibiotics is associated with childhood asthma and childhood obesity.^{14 15} It is recently found that prenatal exposure to antibiotics can probably lead to alterations in the differential methylation at regulatory regions of imprinted genes.¹⁶



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Ms Dominique Esmée Werter; d.e.werter@amsterdamumc.nl

If we can improve diagnostics and related antibiotic prescribing, we possibly can also influence fetal development and possibly long-term health with the results of this study. All of them impact future healthcare costs. Next to that, if we could decrease the number of tests for an accurate diagnosis, costs could be saved.

In the non-pregnant population, a diagnostic test to confirm the diagnosis of UTI is not always considered necessary, since typical clinical symptoms such as dysuria and urgency are regarded distinctive enough.^{7 17–20} In pregnancy, the diagnosis of a UTI is less well studied and more challenging. First of all, many women during pregnancy experience symptoms that mimic a UTI such as frequency as a result of pressure of the baby's head on the bladder.^{8 21} On the other hand, symptoms of a UTI can be aspecific in pregnancy; UTIs in pregnant women may solely present with abdominal pain or Braxton Hicks contractions.^{9 21} All this makes it more difficult to distinguish between asymptomatic bacteriuria (ASB) and UTI. Furthermore, in pregnancy, ASB can also be present: bacteriuria without any UTI signs or symptoms. ASB is not an active infection and the risk of adverse outcomes like preterm birth is low or absent compared with UTIs.^{11 22}

Most hospital protocols recommend testing pregnant women for a UTI when they present with symptoms suggestive of UTI or in case of symptoms suspicious of threatened preterm birth. In the diagnostic work-up, various methods are used: urine dipstick test, urine sediments and bacterial cultures, which are used in various ways and come with several limitations.

First, a urine dipstick is a strip with different reagents present. The reagents react on the presence of certain substances, for example, protein, glucose, nitrite and leucocyte esterase. The most important parameters to diagnose UTI on a dipstick are nitrite and leucocyte esterase. Many gram-negative bacteria produce the enzyme nitrate reductase, which converts urinary nitrate into nitrite indicating the presence of bacteria.²³ In the adult population, the sensitivity of nitrite dipstick reported in a systematic review is 0.54 (CI 0.44 to 0.64), the specificity is 0.98 (CI 0.96 to 0.99), positive likelihood ratio of 29.3 (CI 14.4 to 59.7) and a negative likelihood ratio of 0.48 (CI 0.37 to 0.62). Eight out of 14 of the studies included in this review reported on pregnant women, but none of them reported on symptomatic women.²⁴ Another study shows that the sensitivity and specificity of nitrite to test for ASB in pregnant women are, respectively, 0.55 (95% CI 0.42 to 0.67) and 0.99 (95% CI 0.98 to 0.99).²⁵

Leucocyte esterase is an enzyme released by neutrophils and macrophages. The leucocyte dipstick has a sensitivity of 0.72 (0.61 to 0.84) and a specificity of 0.82 (0.74 to 0.90), and a positive likelihood ratio of 4.87 (3.26 to 7.29) and a negative likelihood ratio of 0.31 (0.18 to 0.51) in the adult population.²⁴

Physiological pyuria can appear in pregnant women.²⁶

Second, for urine sediments, urine samples are centrifuged to obtain a sediment including red and white blood cells, squamous cells and bacteria, which are counted

automatically by microscopy.¹⁶ For a UTI, both the presence or absence of leucocytes and bacteria are of interest. A systematic review in the general population reported a sensitivity range of 57.1%–97%, a specificity of 27.0%–97.0%, a positive likelihood ratio of 1.59–24.57 and a negative likelihood ratio of 0.07–0.655 in studies where they used the sediment.²⁷ Yet again, physiological pyuria can appear in pregnant women.²⁶ The advantage of the urine sediment over the urine dipstick is that the urine sediment counts all bacteria. The urine dipstick only indicates if there are nitrite-forming bacteria present. However, not all bacteria are uropathogenic.

Finally, the reference test to detect a UTI is a urine culture, which determines bacterial growth. However, the urine dipstick takes a few minutes, the urine sediment about an hour and the urine culture at least 24 hours up to 5 days.

The exact number of bacteria present in urine to define a 'positive' urine culture and a UTI is not clear cut. The most common definition is $\geq 10^5$ colony-forming units (CFU)/mL of uropathogens.²⁸ However, the cut-offs used in practice range from $\geq 10^3$ CFU/mL to $\geq 10^5$ CFU/mL.^{18 29 30}

The Dutch guideline of obstetrics and gynaecology recommends performing both a nitrite dipstick and a urine culture when pregnant women present with UTI symptoms. In case of a positive nitrite dipstick, treatment should start immediately. In case of a negative nitrite dipstick, treatment should only be started if the culture is positive. The role of the other diagnostic methods is unclear.⁹ The Dutch general practitioners' guideline recommends performing a nitrite dipstick. In case of a positive nitrite dipstick, people will be treated for UTI. Leucocyte esterase test will be performed when the nitrite result is negative. Urine sediments are recommended if leucocyte esterase is present since a positive result of leucocyte esterase is considered as insufficient proof of a UTI. When either the nitrite or the sediment is positive, treatment should be started. When the leucocyte esterase dipstick is negative but there is still a suspicion for a UTI, a sediment is performed additionally. When both urine dipstick and sediment are negative, a UTI is ruled out. If either urine dipstick or sediment results are positive, a urine culture is performed while antibiotics are directly initiated, awaiting the urine culture results.³¹

Both in the UK and the USA, guidelines do not state the diagnostic work-up for UTIs in pregnancy (Royal College Obstetricians and Gynaecologist (RCOG) guideline, National Institute for Health and Care Excellence (NICE) guideline and American College of Obstetricians and Gynecologist (ACOG) guideline).

Despite the differences in guidelines, in daily practice, the urine is often only tested with a dipstick. In case of a negative test result, often no additional tests are done. The approach when to perform a sediment or a urine culture is equally ambiguous. There is no clear evidence that the diagnostic accuracy of a standalone dipstick urine (including both the presence of nitrite and leucocyte

esterase) is equal to a combined approach of urine dipstick and sediment to diagnose a UTI in pregnancy. Furthermore, pyuria can be present in pregnant women without a UTI.²⁶ Moreover, the additional value of a urine culture in all women, as recommended by the Dutch guideline of obstetrics and gynaecology, is also unknown. For something as common as a UTI during pregnancy, it is undesirable that the available evidence is too limited to properly inform (diagnostic) guidelines, which results in great diagnostic variation, and potential harmful over-treatment and undertreatment.

METHODS AND ANALYSIS

This study aims to evaluate the diagnostic accuracy of urine dipstick analysis and urine sediment to bacterial cultures in the diagnosis of UTI in pregnant women.

Study design

This study is a single-centre prospective cohort study.

Participants

All consecutive pregnant women attending the outpatient clinic, the pregnancy ward or emergency department for women's health in the Amsterdam UMC with symptoms warranting a diagnostic work-up to rule out a UTI can be included, after oral and written consent. These symptoms include dysuria, urgency, frequency, fluid loss, difficulties with voiding, painful voiding, haematuria, or aspecific abdominal pain, (Braxton Hicks) contractions and vaginal blood loss.^{7,9}

Exclusion criteria are a previous UTI episode in the past 2 weeks, antibiotic use in the past 2 weeks or a structural abnormality of the urogenital tract.

Inclusion of women in the study takes place since 1 November 2021. We plan to include all women in the study in 3 years.

Test methods

The urine samples will be clean-catch midstream urine samples. The index test will be a urine dipstick and a urine sediment. The dipstick that we will use is Clinitek novus 10 (Siemens). The urine sediment will be checked with Atellica 1500 Siemens. For both the urine dipstick and the urine sediment, different cut-offs will be used to investigate which cut-off has the best diagnostic value (table 1).

The reference test will be a urine culture.

No blinding will take place for the different tests. The outcome of the test has no influence on the treatment and is necessary for daily practice.

Because of the difficulties to distinguish between ASB and UTI, we will use a different definition for UTI than commonly used. We would like to make sure that we are dealing with a UTI and not ASB.

In this study, a 'true UTI' is present when the following three criteria are met:

1. Presence of at least two specific or non-specific symptoms of a UTI.²⁶
2. A positive urine culture.
3. Symptom improvement during adequate antibiotic treatment, where adequate treatment is defined by proven susceptibility of isolated uropathogens to the administered antibiotic.

The definition of a positive culture is:

1. Urine with $\geq 10^3$ CFU/mL of a uropathogen.

Table 1 Expected outcomes

Test	Determination	Cut-off point	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	
Urine dipstick	Nitrite	Positive (> 10^5 /mL)							
		Leucocyte esterase							
		1+							
		2+							
		3+							
Urine sediment	Bacteria	1+							
		2+							
	Leucocytes	<10/ μ L							
		>10/ μ L							
		>20/ μ L							
		>30/ μ L							
		>40/ μ L							
		>50/ μ L							
>60/ μ L									

2. Maximum of two uropathogens $\geq 10^3$ CFU/mL present. When there are more than two uropathogens present of $\geq 10^3$ CFU/mL, the culture will be considered as contaminated.

Next to that, the woman will be asked to fill out a questionnaire. The questionnaire contains questions about risk factors for UTI and possible clinical symptoms of a UTI. After 5–8 days, when the result of the culture will be available, the woman will be called to evaluate the presenting symptoms. This check-up is part of standard care. Both the woman and the clinician have access to the test result; it is not blinded. Women will be asked permission to collect data from the midwife, gynaecologist or general practitioner about their pregnancy and delivery.

Analysis

The statistical analysis will be performed using IBM SPSS Statistics V.26.

Primary outcome

We will determine which combination of leucocyte esterase, nitrite presence in the dipstick and bacteria presence and leucocyte count in the sediment yield the best performance of both methods separately and combined to predict a 'true UTI' according to our definition. Different cut-offs and combinations of cut-offs of the urine analysis components will be explored to calculate sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios (table 1). In addition, we aim to develop a diagnostic model based on all available evidence on leucocyte esterase, nitrite presence, bacteria presence, leucocyte count and symptoms.

After the best performing cut-offs for both urine dipstick and urine sediment have been determined, we will compare the performance of these two tests together in terms of sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios. Urine culture will be used as the reference test. The performance will be compared with the predefined 'true' UTI. To do this, we first select all true positives and true negatives using the reference test. In addition, we compare the classifications of urine dipstick with urine sediment in a 2x2 table for true positives (sensitivity) and a 2x2 table for true negatives (specificity) and calculate a p value for the difference in classification using a paired McNemar test.

Planned sensitivity analyses will also be performed for different cut-off values for pathogens in urine cultures $\geq 10^3$ CFU/mL, $\geq 10^4$ CFU/mL and $\geq 10^5$ CFU/mL.

Contaminated urine cultures will be considered as negative cultures.

Secondary outcome

We will evaluate which clinical symptoms are best at predicting a UTI in pregnancy and which symptoms are not. The symptoms of a UTI will be studied with incidences and p values to identify which symptoms are associated with UTI.

To identify risk factors for UTI, univariate logistic regression will be used. In case it is possible, multivariate logistic regression will be used to identify the risk factors. We will use a forward stepwise selection for our regression model.

Pregnancy duration will be measured in weeks and days of gestational age and will be compared between women with and without UTI with a Student's t-test.

The timing of the performed urine test (urine dipstick, urine sediment and urine culture) and the gestational age of delivery will be noted. Time between diagnosis of UTI and delivery will be compared using Kaplan-Meier survival curve.

Power analysis

To provide an estimated sample size, we calculated the sample sizes necessary for 80% power in a McNemar paired test comparing urine dipstick with urine sediment in women with true-positive UTI (sensitivity) and true-negative UTI (specificity). The expected discrepant cells for sensitivity are 14% and 5%, with a calculated 181 true-positive cases necessary for 80% power. The expected discrepant cells for specificity are 10% and 4% with a calculated 302 true-negative cases necessary for 80% power. We expect that around 30% of the included women will have a UTI such that the necessary sample size to include is 603 for sensitivity and 432 for specificity.

With a 10% expected drop-out, the sample size would be 660 pregnant women.

Data will be collected using Castor, which is an application system that enables collection and clean-up of trial data using the internet. Data handling will be done coded. The data will be saved for 15 years.

Patient and public involvement

There was no patient or public involvement in this research.

Ethics and dissemination

Approval was requested from the Medical Ethics Review Committee of the Academic Medical Centre; an official approval of this study by the committee was not required (METC review number W21_291 #21.318). All participants will give written and oral informed consent prior to entry to the study and will be made aware that participation is strictly voluntary.

The outcomes of this study will be published in a peer-reviewed journal.

DISCUSSION

The diagnostic accuracy of a urine dipstick and, less often, a urine sediment for the diagnosis of bacteriuria in pregnancy has been evaluated.^{23 35} However, no studies are available in pregnant women on the diagnostic accuracy of symptomatic UTIs. As a result, different guidelines in the Netherlands advise different ways of testing for UTIs in pregnant women. International guidelines lack

any recommendations on specific urine tests. However, in pregnant women with a UTI, both undertreatment and overtreatment are potentially harmful; therefore, correct diagnosis is very important.

Bias

The focus of this study is the diagnostic work-up. We will not intervene in the treatment given or follow-up provided to the participating women. It is likely that certain types of bias will be introduced as a result of implementation of this study. Bias could be introduced because more diagnostics will be performed and all three urine test results will be reported to the treating clinician (not blinded). Since more result will be available, this could affect the prescription of antibiotics.

We do not expect a lot of women with partial verification bias since the three different urine tests will be most of the time executed at the same time from the same urine sample. Because of this, we avoid that only the urine dipstick and/or sediment is performed and the urine culture is not executed.

The urine culture has been used, both in daily practice and in research, for a long time. There are no logical alternative reference standards. The urine culture has been proven to be effective. We do not expect an inappropriate reference standard.

Since the result of the urine culture is only available a few days after the results of the urine dipstick and sediment, we do not expect a review bias.

Clinical impact

Due to the different cut-offs to report uropathogens and their susceptibilities (10^3 instead of 10^4), the rate of prescribing antibiotics may increase too. However, the result of the culture will only come in after a few days, so the decision to start antibiotics has most likely already been made. With this study, we hope to provide either better evidence for the current advice in guidelines and/or guide necessary adjustments.

CONCLUSION

To avoid unnecessary treatments, diagnostic tests and costs, and to minimise possible harmful neonatal outcomes, the diagnostic process of UTIs should be optimised. This new workflow should be implemented in the daily care to create a more evidence-based treatment strategy. Since the diagnostic work-up for UTIs takes place on a daily basis, the results of this research will have a major impact on daily routine care. To find an optimal strategy for diagnosing a UTI is only the start of tackling the challenges around the diagnosis of UTIs in pregnancy.

Author affiliations

¹Department of Obstetrics and Gynaecology, University of Amsterdam, Amsterdam, The Netherlands

²Department of Obstetrics and Gynaecology, Amsterdam University Medical Centres, Duivendrecht, The Netherlands

³Department of Clinical Chemistry, University of Amsterdam, Amsterdam, The Netherlands

⁴Department of Microbiology, University of Amsterdam, Amsterdam, The Netherlands

⁵Obstetrics and Gynaecology, Amsterdam UMC Location AMC, Amsterdam, The Netherlands

⁶Department of Microbiology, Amsterdam UMC-Location AMC, Amsterdam, The Netherlands

⁷Center for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands

Contributors DEW wrote the proposal and the manuscript. BMK initiated the research, and critically revised the proposal and manuscript. EvL critically revised the proposal and manuscript. MCFJdR critically revised the manuscript. SDK critically revised the proposal and manuscript. EP critically revised the proposal and manuscript. CS critically revised the proposal and manuscript. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Dominique Esmée Werter <http://orcid.org/0000-0003-3121-0441>

REFERENCES

- Amiri M, Lavasani Z, Norouzirad R, *et al*. Prevalence of Urinary Tract Infection Among Pregnant Women and its Complications in Their Newborns During the Birth in the Hospitals of Dezful City, Iran, 2012 - 2013. *Iran Red Crescent Med J* 2015;17:e26946.
- Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med* 2002;113 Suppl 1A:5-13.
- Mazor-Dray E, Levy A, Schlaeffer F, *et al*. Maternal urinary tract infection: is it independently associated with adverse pregnancy outcome? *J Matern Fetal Neonatal Med* 2009;22:124-8.
- Schieve LA, Handler A, Hershov R, *et al*. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. *Am J Public Health* 1994;84:405-10.
- Schneeberger C, Erwich JJHM, van den Heuvel ER, *et al*. Asymptomatic bacteriuria and urinary tract infection in pregnant women with and without diabetes: cohort study. *Eur J Obstet Gynecol Reprod Biol* 2018;222:176-81.
- Chen Y-K, Chen S-F, Li H-C, *et al*. No increased risk of adverse pregnancy outcomes in women with urinary tract infections: a nationwide population-based study. *Acta Obstet Gynecol Scand* 2010;89:882-8.
- Pietrucha-Dilanchian P, Hooton TM. Diagnosis, treatment, and prevention of urinary tract infection. *Microbiol Spectr* 2016;4.
- Sobel JD KD. Urinary tract infections.
- NVOG. URINEWEGINFECTIE in de ZWANGERSCHAP 2011.
- Bánhidý F, Acs N, Puhó EH, *et al*. Pregnancy complications and birth outcomes of pregnant women with urinary tract infections and related drug treatments. *Scand J Infect Dis* 2007;39:390-7.
- Kazemier BM, Koningstein FN, Schneeberger C, *et al*. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. *Lancet Infect Dis* 2015;15:1324-33.
- Kenyon S, Pike K, Jones DR, *et al*. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. *Lancet* 2008;372:1310-8.



- 13 Nordeng H, Lupattelli A, Romøren M, *et al.* Neonatal outcomes after gestational exposure to nitrofurantoin. *Obstet Gynecol* 2013;121:306–13.
- 14 Chu S, Yu H, Chen Y, *et al.* Periconceptional and gestational exposure to antibiotics and childhood asthma. *PLoS One* 2015;10:e0140443.
- 15 Mueller NT, Whyatt R, Hoepner L, *et al.* Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *Int J Obes* 2015;39:665–70.
- 16 NHG. *Laboratoriumdiagnostiek Urineweginfecties (LESA)*, 2020.
- 17 Giesen LGM, Cousins G, Dimitrov BD, *et al.* Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. *BMC Fam Pract* 2010;11:78.
- 18 Schmiemann G, Kniehl E, Gebhardt K, *et al.* The diagnosis of urinary tract infection: a systematic review. *Dtsch Arztebl Int* 2010;107:361–7.
- 19 Kranz J, Schmidt S, Lebert C, *et al.* The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1. *Urol Int* 2018;100:263–70.
- 20 Geerlings SE. Clinical presentations and epidemiology of urinary tract infections. *Microbiol Spectr* 2016;4.
- 21 Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. *Am J Obstet Gynecol* 2018;219:40–51.
- 22 Smaill FM, Vazquez JC, Cochrane Pregnancy and Childbirth Group. Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2019;2019:11.
- 23 Gieteling E, van de Leur JJCM, Stegeman CA, *et al.* Accurate and fast diagnostic algorithm for febrile urinary tract infections in humans. *Neth J Med* 2014;72:356–62.
- 24 St John A, Boyd JC, Lowes AJ, *et al.* The use of urinary dipstick tests to exclude urinary tract infection: a systematic review of the literature. *Am J Clin Pathol* 2006;126:428–36.
- 25 Rogozińska E, Formina S, Zamora J, *et al.* Accuracy of Onsite tests to detect asymptomatic bacteriuria in pregnancy: a systematic review and meta-analysis. *Obstet Gynecol* 2016;128:495–503.
- 26 Kouri TT, Gant VA, Fogazzi GB, *et al.* Towards European urinalysis guidelines. introduction of a project under European Confederation of laboratory medicine. *Clin Chim Acta* 2000;297:305–11.
- 27 Beyer AK, Currea GCC, Holm A. Validity of microscopy for diagnosing urinary tract infection in general practice - a systematic review. *Scand J Prim Health Care* 2019;37:373–9.
- 28 Kass EH. Pyelonephritis and bacteriuria. A major problem in preventive medicine. *Ann Intern Med* 1962;56:46–53.
- 29 Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. *JAMA* 2014;311:844–54.
- 30 Aspevall O, Hallander H, Gant V, *et al.* European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. *Clin Microbiol Infect* 2001;7:173–8.
- 31 Bouma MGS, Klinkhamer S, Knottnerus BJ. *Urineweginfecties*. NHG, 2020.
- 32 Devillé WLJM, Yzermans JC, van Duijn NP, *et al.* The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol* 2004;4:4.