Asymptomatic bacteriuria and urinary tract infections in women
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chapter TEN

Discussion
Background of screening policies: Wilson and Jungner criteria

Screening is a valuable tool and may lead to early detection and treatment of disease, preventing subsequent disease and disease related sequelae. Unfortunately screening, like any other treatment, has the potential to do harm. Therefore, the evaluation of a screening programme is a delicate process weighing desirable and undesirable consequences.\(^1,2\)

The Wilson and Jungner criteria were published almost 50 years ago in a report entitled ‘Principles and practice of screening for disease’.\(^1\) To date these criteria are still valuable landmarks for the decision making process to select and introduce an effective screening programme.

Preventing disease and subsequent complications in a newborn with a future life is possibly one of the highest attainable goals in public health. Preterm birth (< 37 weeks’ gestation) is the pre-eminent cause of perinatal mortality and morbidity in developed countries.\(^3\) During the past decades several attempts have been made to reduce preterm birth with the use of screening (& treatment) programmes such as screening of cervical length and infectious diseases.\(^4,5\)

Colonization and related infections of the urinary tract have explicitly been identified as one of the risk factors for preterm birth with potential lifelong sequelae.\(^3,6\) Asymptomatic bacteriuria (presence of bacteria in urine without symptoms of a urinary tract infection) was considered the pre-clinical and possibly also pre-pathological stage of symptomatic urinary tract infections including pyelonephritis.\(^3,6\) However this assumption is now being questioned.

Around the same time as the landmark publication describing the Wilson and Jungner criteria ASB screening programmes were considered and introduced in developed countries to prevent pyelonephritis and/or preterm birth.

In this thesis a number of aspects related to ASB and UTI have been investigated in three patient groups; women with diabetes mellitus (DM), pregnant women and pregnant women with DM. The experiences gained while performing the studies in combination with the results found formed the foundation for the main question of this discussion: is screening for ASB during pregnancy to prevent pyelonephritis and preterm birth desirable? To address this question the Wilson and Junger criteria will be applied (see Figure 1).
The condition

1. The condition sought should be an important health problem
2. The natural history of the condition should be adequately understood
3. There should be recognisable latent or early symptomatic stage

The treatment and test

4. There should be an accepted treatment for patients with recognized disease
5. There should be an agreed policy on whom to treat as patients
6. There should be a suitable test
7. The test should be acceptable to the population
8. Facilities for diagnosis and treatment should be available

The costs

9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

The screening programme

10. Case-finding should be a continuing process and not a “once and for all” project
11. There should be a defined target population (revised)
12. There should be scientific evidence of screening programme effectiveness (revised)
13. The overall benefits of screening should outweigh the harm (revised)

The condition

For the purpose of this discussion the two following criteria are combined:

The condition sought should be an important health problem (1) and the natural history of the condition, including development from latent to declared disease, should be adequately understood (2)

The condition we seek to prevent is preterm birth, which potentially caused by colonization and/or infections of the urinary tract during pregnancy.\textsuperscript{3} ASB was considered the latent stage, UTI the early symptomatic stage and pyelonephritis the late complicated stage of disease.\textsuperscript{6-10} This assumption is reconsidered as described above. The hypothesis is that by screening and treating for ASB during pregnancy primarily the risk for developing pyelonephritis is reduced and subsequently the risk for preterm birth.\textsuperscript{7,9-11} However, both the importance and the natural history of colonization and subsequent infections of the urinary tract and/or preterm birth are ambiguous.

Preterm birth

The exact etiology of preterm birth is poorly understood and thought to be the result of a combination of physiopathological, genetic and environmental factors.\textsuperscript{3} To the best of our knowledge, there is no experimental evidence supporting the direct relation between colonization of the urinary tract and preterm birth. It has been hypothesized that certain bacterial products including endotoxins and/or phospholipases influence the synthesis of prostaglandins, important mediators of uterine activity.\textsuperscript{12}
Asymptomatic bacteriuria, pyelonephritis & preterm birth
In pregnant women ASB prevalence between 2% and 10% have been reported.\textsuperscript{13,14} Pregnant women are more prone to develop ascending UTI because up to 90% of pregnant women develop dilatation of the renal system in combination with decreased peristalsis of the ureters and bladder facilitating bacterial colonisation and ascending infection in pregnancy.\textsuperscript{15} Studies from the 60s, 70s and 80s show that around 30% to 40% of pregnant women with untreated ASB developed pyelonephritis compared to less than 2% of those without ASB.\textsuperscript{8,14,16-18} The consequences of not treating ASB on preterm birth are less well established.\textsuperscript{7} A meta-analysis of 11 randomized or quasi-randomised control trials showed that the incidence of pyelonephritis was reduced in pregnant women with ASB who were treated with antibiotics compared to those who were not treated with antibiotics (relative risk (RR) 0.23, 95% confidence intervals (CI) 0.13 to 0.41) and that treatment of ASB with antibiotics was associated with reduced incidence of low birthweight babies (RR 0.66, 95%-CI 0.49 to 0.89).\textsuperscript{7} However, no differences were found in preterm birth. The authors concluded that the overall quality of the studies were poor.\textsuperscript{7} Moreover most trials were performed more than 25 years ago, before the widespread use of the ultrasound to measure the duration of pregnancy.\textsuperscript{19} Therefore, more timely studies are urgently needed.
Two of our studies (‘Pregnancy, ASB & UTI’ (PRABUTI) study Netherlands and PRABUTI Australia) described in chapter 8 and 9 provide up-to-date numbers on the prevalence ASB in pregnant women in two developed countries. The found that prevalence of ASB in pregnant women with and without diabetes mellitus varied between 4.7% and 2.3% in the Netherlands (no ASB screening programme in place) and 5.6% and 3.7% in Australia (ASB screening programme in place). In the PRABUTI study performed in the Netherlands no association was found between ASB and UTI including pyelonephritis or adverse pregnancy outcomes even though women with ASB were not treated. Study urine culture results were kept anonymised since currently screening for ASB is not part of standard care in the Netherlands. It has been noted that the number of ASB cases was limited and the study sample small, therefore, only able to detect large differences. The results of the ‘ASB screen and treat’ study described in chapter 7 will be available in the near future. For this prospective cohort study more than 5,000 pregnant women were screened for ASB in the Netherlands. For the ASB treat study ASB positive women were randomised for treatment with nitrofurantoin or placebo. This study will provide important up-to-date data on the prevalence of ASB, association with pyelonephritis and/or preterm birth and the effectiveness of an ASB screening and treatment programme in pregnant women to prevent pyelonephritis and/or preterm birth.

Urinary tract infection & preterm birth
Accurate data to estimate the incidence of UTI in pregnant women are missing. Studies report an UTI incidence varying around 2% (culture confirmed UTI) to 15% (ICD episodes collected by a health maintenance organization).\textsuperscript{9,20,21} The lack of information on incidence of UTI during pregnancy was one of the reasons to perform both PRABUTI studies (described in chapter 8 and 9) showing an incidence of UTI between 4.7% in pregnant women with and 11.2% in women without DM in Australia (definition based on physician diagnosis) and 16.8% in pregnant women with and 12.9% in women
without DM in Netherlands (definition based on antibiotic prescription). Our studies revealed possible reasons why accurate data on UTI incidence are missing. Some symptoms of UTI such as urgency and frequency are also common pregnancy complaints, which can make it more difficult to recognize a UTI and to distinguish between ASB and a symptomatic UTI. Additionally, treatment of a UTI is often commenced based on symptoms before proper diagnostics are performed, distorting the ‘true’ incidence of UTI. In the PRABUTI study performed in Australia a lower incidence of culture confirmed UTI was found compared to the incidence of clinical UTI; 2.8% in women with and 3.7% in women without DM.

In both PRABUTI studies no association was found between UTI and preterm birth. Another larger retrospective population based study from Israel showed that a UTI (positive urine culture in a woman with symptoms of dysuria, urgency and frequency) during pregnancy is independently associated with preterm birth (15.1% vs. 7.8%).

Pyleonephritis & preterm birth
Pyelonephritis was estimated to occur in 2% of pregnancies with a recurrence rate up to 23% within the same pregnancy or soon after birth. Recent studies showed that the incidence of antepartum pyelonephritis, often defined as a hospital admission for a UTI, has decreased in developed countries, now estimating an incidence of antepartum pyelonephritis between 0.07% and 0.5%. The reduction may have various reasons including the introduction of ASB screening programmes and/or improved antenatal care. These recent studies concluded once more that antenatal pyelonephritis is associated with preterm birth (10.3%-20% versus. 7.8%-7.9%).

However, the percentage of preterm births directly attributable to pyelonephritis (the number, which can be prevented when the incidence of antenatal pyelonephritis is reduced to zero) is uncertain since both conditions (pyelonephritis and preterm birth) have overlapping risk factors and possibly even a common cause.

In conclusion, we can discuss whether the presence of ASB and the development of UTI in pregnant women is an important health problem; nonetheless, many questions concerning the natural history of the condition, including development from latent to declared disease (pyelonephritis and/or preterm birth), remain and are not adequately understood.

There should be a recognizable latent or early symptomatic stage (3)

ASB when considered as latent stage and UTI as an early symptomatic stage, are both recognizable conditions that may be associated with an increased risk of adverse pregnancy outcomes. However, ASB is an asymptomatic stage and not necessarily a latent stage since only a small percentage of pregnant women with ASB develop one of the associated diseases; symptomatic lower UTI, pyelonephritis and/or preterm birth.

Moreover, most of the pregnant women who developed a symptomatic UTI did not suffer from bacteriuria at the moment of screening (often performed in the first half of pregnancy). In an old study by Lawson and Miller they reported that only 19.1% of pregnant women who developed symptomatic urinary tract infection had bacteriuria
on initial screening. In our retrospective PRABUTI study performed in Australia none of the pregnant women who developed UTI had bacteriuria on initial screening. In our prospective study performed in the Netherlands only one of the 20 women who had either positive week 12 or week 32 samples developed a UTI during pregnancy.

Another key issue while discussing the value of this criterion is that ASB is not a permanent stage since ASB can dissolve spontaneously. Long-term follow-up studies of untreated ASB are mainly performed in non-pregnant patients with DM. A study with an 18 months follow-up period showed an increased incidence of UTI in women with type 2 DM and ASB compared to those without ASB at baseline (34% vs. 19%) and comparable incidence of UTI in women with type 1 DM and ASB compared to those without DM (12% vs. 15%). Even though an increased incidence of symptomatic UTI in women with ASB was found, still only one third of the women with ASB developed a symptomatic UTI. Moreover, a study by Nicolle and colleagues demonstrated that many women have intermittent ASB, either spontaneously or due to antibiotic treatment.

Most of these (long) term ASB follow-up studies were performed in non-pregnant women, and thereby the duration of a pregnancy is limited. In our prospective study (PRABUTI Netherlands) pregnant women with and without DM provided a urine sample at 12 and 32 weeks’ gestation. Only two out of 12 women (who collected two samples) had a positive urine culture result at 12 and 32 weeks’ gestation. An old study from Gower et al. reported that of the 164 women who had bacteriuria during pregnancy, six to twelve months after pregnancy a quarter of these women still suffered from bacteriuria independently of antibiotic treatment.

The changeable nature of the presence of bacteriuria makes it difficult to determine when pregnant women should be screened for ASB. In most countries screening takes place early in pregnancy. For a study by Stenqvist et al. they screened 3,254 pregnant women at each prenatal visit (minimal three visits) showing that the risk of bacteriuria increased from 0.8% at 12 weeks’ gestation to 1.93% at the end of pregnancy. They recommend screening for ASB around the 16th week of pregnancy. McIsaac et al. showed that a urine culture before 20 weeks’ gestation only detected half of the ASB cases of all cases identified with three urine cultures: at fewer than 20 weeks’, at 28 weeks and 36 weeks’ gestation. This study did not assess the association between one, two or three urine cultures and pyelonephritis or preterm birth.

The varying course of ASB in combination with the limited evidence for associations with negative long-term effects support the hypothesis that ASB is more likely a commensalism state than a disease. It is not clear whether a recognizable latent or early symptomatic stage for pyelonephritis or preterm birth is present.

The treatment

There should be an accepted treatment for patients with recognized disease (4)

Currently the most common way to treat both asymptomatic colonization (ASB) and symptomatic infections (UTI and pyelonephritis) of the urinary tract are antibiotics. The ability of antibiotics to restrain the growth or kill microorganisms causing infections of the urinary tract depends on the concentration of the antimicrobial achieved in the
urine together with the sensitivity of the organisms to that antibiotic.\textsuperscript{33,34} Although a Cochrane meta-analysis showed that antibiotic treatment of ASB compared to no treatment (placebo) reduced the incidence of pyelonephritis with a reduction varying between 1\%-4\% to 20\%-35\%.\textsuperscript{7,13} Treatment of ASB with antibiotics did not lead to reduction in preterm birth. Moreover treatment of ASB with antibiotics does not always lead to a disease free interval, in this case pregnancy due to relapse or recurrence of ASB.\textsuperscript{29,30}

A present issue that may have an effect on antibiotic treatment of ASB and prevention of other infectious diseases including clinical UTIs is the increasing prevalence of antimicrobial resistance.\textsuperscript{35} Antibiotics can only reduce the presence of microorganisms when the present microorganism is sensitive to the given antibiotic.\textsuperscript{33,34} Screening for ASB and subsequent treatment with antibiotics may cause an increase of the use of antibiotics, especially if the number needing treatment is high. This again may subsequently undermine the effectiveness of the screening programme because one of the main causes of antimicrobial resistance is the overuse of antibiotics.

But what should a clinician prescribe when ASB is present? A Cochrane review addressing antibiotic regimens for treatment of ASB in pregnancy could not draw any definite conclusion based on the five included studies.\textsuperscript{36} Another Cochrane review on the duration of treatment of ASB during pregnancy analysing 13 studies could only conclude that a single-dose treatment of antibiotics may be less effective than a seven-day treatment. However, a single-dose regimen was associated with less side-effects. The authors note that the overall quality of included trials was low.\textsuperscript{37}

So far we are only talking about antibiotics and not about an optimal and acceptable treatment of ASB in pregnant women. Many other interventions have been proposed to treat bacteriuria including cranberry products, probiotics and behavioural interventions.\textsuperscript{38} Firstly, not all antibiotics may be safe to use during (certain stages of) pregnancy. Secondly, antibiotics may cause several side-effects such as gastro-intestinal symptoms and vaginal candidiasis.\textsuperscript{38,39}

Another important factor to consider that may possibly influence the adherence and therewith the acceptability to either pharmacological or non-pharmacological interventions is the presence of nausea and vomiting, common in pregnancy due to physiologic changes in pregnancy.\textsuperscript{40} Only a limited number studies investigating the effectiveness of alternative interventions have been performed.

We performed a Cochrane review entitled interventions for preventing recurrent urinary tract infections during pregnancy. Only one trial was identified comparing a daily dose of nitrofurantoin and close surveillance with close surveillance alone not showing an effect of the additional nitrofurantoin (see chapter 6). This review reveals that close surveillance may be a way to prevent recurrent UTI.

One of the possible non-pharmacological interventions is cranberry products.\textsuperscript{41} So far little evidence of the effect and side-effects of cranberry products during pregnancy are known. A meta-analysis of studies in non-pregnant women showed that cranberries are effective in reducing urinary tract infection recurrence (2 trials, sample size 250, RR 0.53, 95\% CI 0.33-0.83).\textsuperscript{41} And currently a Cochrane review is being performed to determine the role of cranberries in the treatment of ASB in pregnant women.\textsuperscript{42} A recent study investigated the safety of cranberry product use during pregnancy using the Norwegian Mother and Child cohort including more than 100,000 pregnancies. No
increased risk for malformations and other adverse pregnancy outcomes were found. Randomised control trials comparing different pharmacological and non-pharmacological interventions are necessary to investigate potentially affective interventions to treat ASB in pregnant women. Moreover, the acceptability of different interventions, including willingness of pregnant women to use the intervention during pregnancy should be investigated.

In conclusion, at this moment it is uncertain if we can consider antibiotics as the accepted treatment for ASB in pregnant women seeing the recent studies on adverse events related to antibiotic use during pregnancy and the limited data on alternative treatments.

There should be an agreed policy on whom to treat as patients (5)

The distinction between significant (disease) and insignificant colonisation (not related with symptoms or adverse events) of the urinary tract often is not clear-cut. Physiological variables tend to distribute around the mean and result in a normal curve. People with the disease represent the extreme end of the curve. The border-line group, presented by the area under the curve in between the pregnant women without the disease and with the disease (right tail of the curve) may be larger due to the bell-curved shape. The variety of definitions and diagnostic criteria used for ASB underscore that it is not clear whom to treat as patients and whom not to. A urine culture is the gold standard used to diagnose bacteriuria. Growth of $10^5$ colony forming units (cfu)/ml of one (or maximum two) uropathogens is a commonly used definition. Some argue that two consecutive urine cultures are desirable, but the interval between the two urine cultures is not clearly defined. In (pregnant) women with complaints of symptomatic UTI, a growth of $10^3$ cfu/mL is considered clinically relevant and considered 'disease'. A similar cut-off point for asymptomatic Group B Streptococcus (GBS) bacteriuria is often used since treatment may be beneficial. Furthermore, it is not clear which microorganisms are considered as uropathogens and which as contaminants in ASB. This probably explains why studies report a wide range of ASB prevalence up to 40%. The most common organism associated with bacteriuria is *Escherichia coli*. Examples of microorganisms alternately defined as uropathogen are coagulase negative staphylococci (CNS) and *Acinobacter* spp. Summarizing, currently it is not certain whom to treat as a patient and whom not to, meaning this criteria is not met. Before introducing a screening and treatment programme a clear definition with clinical relevance should be identified. An internationally used definition of ASB would be a possible way to make data on ASB more comparable which may facilitate a more evidence based decision as to if an ASB screening programme is needed in pregnant women.

To be able to draft a clinically relevant definition of ASB, we mean that investigating the risk for adverse pregnancy outcomes related to different cut-off points for the definition of a positive urine culture, including lower cut-off points (e.g. $10^3$ cfu/mL) is desirable. Since at present in most developed countries an ASB screening and treatment policy is in place (standard care) it may be considered unethical to investigate the association
between untreated ASB and adverse pregnancy outcomes. However, the association between low-colony count bacteria and adverse pregnancy outcomes can be investigated since in most countries only a growth of \( \geq 10^5 \) cfu/mL is considered clinically relevant and therefore treated.

The test used in screening

Two criteria combined; there should be a suitable test or examination (6) and the test should be acceptable to the population (7)

A urine culture is considered the gold standard for diagnosing bacteriuria.\(^33\) The biggest challenge related to the diagnosis of ASB (and UTI) is differentiating between true bacteriuria and contamination.\(^{14}\) Schnarr et al. wrote the following: ‘The original criterion for diagnosing ASB was \( \geq 10^5 \) cfu/mL of a single uropathogen in two consecutive samples with a 95% probability that the woman has true bacteriuria. The detection of \( \geq 10^5 \) cfu/mL in a single voided midstream urine is accepted as a more practical and adequate alternative although there is only an 80% probability the woman has true bacteriuria’.\(^{14}\)

But does ‘true’ bacteriuria exist and is it possible to distinguish ‘true’ bacteriuria from contamination? Urine itself is considered to be sterile (when bacteriuria is not present) conversely; the urethra (the tube that drains urine from the bladder) and the vaginal and perineal skin surrounding the urethra are known to be colonized with a motley crew of commensal bacteria.\(^ {45}\) These bacteria are often considered as non-pathogens, bacteria that do not cause infection or disease, however when these bacteria are introduced in a different environment like the bladder (via the urethra) they can become pathogens (uropathogens). Especially in women, who have a short urethra compared to men, bacteria present on the vaginal and perineal skin can easily enter and colonize the urinary tract.\(^ {45}\)

The term bacteriuria implies that it includes all bacteria found in urine (sample). Ideally the term bacteriuria should be used to refer to bacteria cultured in a urine sample that originate from the urinary tract including bladder and kidneys. A possible way to improve the validity (the ability to separate those with disease from those without disease) of a urine culture is a proper urine sample. It was hypothesized that more elaborate sampling methods such as midstream clean-catch urine sample and collection of the first concentrated urine sample in the morning help minimizing contamination compared to midstream sample. However, in our study we found comparable contamination rates after using all three sample collection methods (chapter 5).

Moreover, a high prevalence of clinically irrelevant quantities of contamination (>80% contained skin flora) was found by analysing urine samples using both Gram stain or urine culture to analyse samples. When the bacteria (skin flora) normally defined as contaminants may overgrowth a possible present uropathogen it might become more difficult to distinguish between ‘true’ bacteriuria and contamination. This may happen when the urine for example was not examined in a timely fashion or refrigerated.
Other urine sample techniques that could possibly reduce contamination, which in general are not considered acceptable, are urine collection after catheterization or bladder puncture.\textsuperscript{45,46} With these methods the vaginal and genital skin full of skin flora are by-passed minimizing contamination with skin flora, though both methods are less comfortable for women and may introduce bacteria in the bladder. In general when, a test used for a screening programme is less accepted by the population, the uptake of the screening programme is lower.\textsuperscript{1}

Finally, performing a urine culture is more expensive and demands more manpower than rapid dipstick tests, which are often used in more resource-poor settings. A dipstick test contains several pads of reagents for detecting the presence of leucocytes and/or nitrite, which react (change colour) when brought into contact with urine.\textsuperscript{45} The downside of dipsticks for diagnosing ASB is the poor positive and especially negative predictive value possibly leading to over-treatment and under-treatment.\textsuperscript{1,36,47} Magnini and colleagues found a positive likelihood ratio for detecting ASB in pregnant women with a dipstick (positive result defined as nitrites or leukocyte esterase or both) of only 6.95 (95% CI 5.80 – 8.33) and a negative likelihood ratio of 0.50 (95% CI 0.54-0.57).\textsuperscript{47} The issues around the collection of ‘suitable’ urine sample (read no contamination) required for unambiguous urine culture results make it especially uncertain whether a suitable test which is acceptable to the population is available.

**Facilities for diagnosis and treatment should be available (8)**

General prerequisites for a diagnostic programme are the presence of a convenient moment to perform the test. The test must be easy to perform, cheap and providing an easy to read and clear answer with unequivocal consequences for follow-up. Numerous screening programmes are in place for pregnant women including infectious diseases such as human immunodeficiency virus (HIV), hepatitis B virus and Treponema pallidum.\textsuperscript{5} Most screening tests are performed around 12 weeks gestation, a suitable environmental opportunity for introducing an additional screening.\textsuperscript{5}

As partly described in the preceding paragraph here are several methods to diagnose bacteriuria. The most common tests used in screening programmes are a urine culture and in more poor resource settings a rapid dipstick test. A urine culture is a basic diagnostic test most likely available at all microbiology laboratories in the Netherlands. As an initial screening test a dipstick test is easier to perform and can be performed by the treating gynaecologists, midwife or even assistant during an antenatal care visit. A possible obstacle to overcome is that it takes time to inform women about the benefits and possible consequences of ASB screening and this time needs to be reserved during one of the already planned antenatal visits. Moreover performing a urine culture is elaborate. Based on the experiences gained while performing the PRABUTI and the CUP study (described in chapter 5, 8 and 9) the collection of a proper urine sample needed for a urine culture is possibly going to be the biggest challenge. Even though pregnant women more often have to pee, peeing on demand is not always possible for every woman, especially since a midstream urine sample is desirable. An alternative option is allowing women bring a urine sample from home, risking improper (not in the fridge, unsterile cup) storage of the sample between peeing and handing it over at the healthcare facility, possibly altering the result the
urine test (overgrowth of contaminants).
The development of new technologies to make the process including urine collection more user-friendly would be worthwhile when considering the introduction of a ASB screening programme. Currently the UriSwab sponge impregnated with boric acid being is investigated. The boric acid preserves the urine which makes it possible to use normal mail to transport the urine sample to the intended laboratory.
Follow-up and treatment of pregnant women with positive urine tests can be performed by the GP or the gynaecologist. Midwives are not certified to prescribe antibiotics in the Netherlands. In the Netherlands, UTI is the most frequent reason for a GP visit during pregnancy. Therefore, training and guiding GPs in the treatment of ASB in pregnant women will be fairly straightforward. Altogether, it seems that facilities for diagnosis and treatment for this disease are available.

The costs

The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole (9)

Preterm birth is extremely costly due to increased maternal and neonatal admissions and will almost always outweigh the costs of a screening programme like ASB screening even with a high number of patients to treat as long as effectiveness of the programme has been shown. Studies showed that the cumulative costs for children born preterm during the first 10 years of life doubled compared those who are born term.
Not only preterm birth but also pyelonephritis in pregnant women is costly since a hospital admission is often needed. Rouse and colleagues concluded based on an analytic decision model that screening for ASB to (only) prevent pyelonephritis with either a urine culture or a leukocyte esterase-nitrite dipstick is cost-effective when the prevalence of ASB is 6% of higher.
An economic evaluation using the ASB-study (chapter 7) screen and treat data will be performed in the near future to evaluate if the costs of screening outweigh the reduction in costs and health benefits. However mainly due to lacking evidence on the effectiveness of ASB screening and treating policies we conclude that it is currently not clear whether the cost of case-finding is economically balanced in relation to possible expenditure on medical care as a whole.

The screening programme

Case-finding should be a continuing process and not a “once and for all” project (10)

This criterion is less applicable since a good antenatal care system, with comprehensive coverage is already present in the Netherlands. In the past screening programmes were often linked to events such as fairs. One of the problems with the single occasion...
screening programmes is that often those at least risk, are attending the screening.

**Emerging screening criteria**

Over the years emerging criteria were developed and in 2008 the WHO proposed eight additional screening criteria. We will address three of the additional criteria since most of the suggested additional criteria concern genetic screening and those are not applicable to the present research question whether screening for ASB in pregnant women is desirable.

**There should be a defined target population (11)**

When introducing a screening programme it is worthwhile to consider if all or only a subgroup of pregnant women needs to be screened and whether it is possible to identify pregnant women with certain risk factors for the presence of ASB. This reason precisely was the impetus for both PRABUTI studies (chapter 8 and 9). One of the risk factors for both ASB and symptomatic UTI is diabetes mellitus (DM). Diabetes mellitus including gestational DM is an increasingly prevalent endocrine disease. Even though earlier studies showed that ASB is more prevalent in non-pregnant women with DM compared to those without DM, both PRABUTI studies did not find a difference in prevalence of ASB and incidence of UTI between pregnant women with DM and pregnant women without DM. These results do not support the introduction of a more ‘selective’ screening programme for only pregnant women with DM. More insight into the natural course of ASB and possibly related consequences may help in identifying other risk factors in order to narrow the target population. One may think of certain types of micro-organisms that predict the progression from ASB into symptomatic UTI and/or preterm birth or underlying abnormalities of the urinary tract. Choosing a proper target population with substantial risks for the disease often improves the effectiveness of the screening programme, but this group is not identified in pregnant women.

**There should be scientific evidence of screening programme effectiveness (12)**

Studies addressing the effectiveness of ASB screening programmes that are nowadays in place in several Western countries are lacking. A screening programme can fulfil all criteria described above but the effectiveness can be limited when “the uptake”, namely the number of women eligible for screening for whom a urine culture result is reported, is low. Barriers for women to attend the screening programme may be stress related to awaiting the result and/or possibly having the ‘disease’, an unwillingness to use antibiotics during pregnancy, or lack of knowledge.

Our retrospective study performed in Australia, where screening for ASB is recommended, provides some insight in the practical implementation and the efficiency of screening and treating policies in pregnant women generally and especially in pregnant women with DM. We found that in most records of pregnant women randomly selected a urine culture was available, however, only in a limited number of women antibiotic treatment was recorded. When an ASB screening programme is present, a
surveillance system should be in place to monitor its quality. To identify barriers to participation, qualitative research such as interviews or focus-groups are preferred. In conclusion, the scientific evidence of this screening programme effectiveness is not clear.

The overall benefits of screening should outweigh the harm (13)

Maybe the most important criterion of the whole list is: ‘Primum non nocere’ or ‘first, do no harm’. Nowadays often referred to as non-maleficence, one of the principles of bioethics is making healthcare workers aware that doing nothing may be better than doing something (treating) when this causes more harm than benefits.1,2 Emerging evidence showing possible long-term consequences of antibiotic use in pregnant women are reason for concern.55-57 Recent studies showed several associations between antibiotics used during pregnancy and adverse neonatal outcomes including increased risk for cerebral palsy, early onset sepsis with antibiotic-resistant micro-organisms, malformations and epilepsy. These side-effects may be worse than the disease, especially since it is not clear that the treatment causing the side-effects is preventing preterm birth.

Not only may the antibiotic treatment cause more harm than good. Since existing diagnostic tests for ASB have less than 100% specificity pregnant women will be diagnosed with ASB while they are not suffering from ASB (false-positive).45,47 This will provoke a “diagnostic odyssey” rather than prevent one and this harm could potentially cause more anxiety than detecting [ASB] could relieve’ as Harris and colleagues state.58

Conclusion

Drastic improvements in health care including antenatal care due to the increasing knowledge and ground-breaking developments have taken place in the last 50 years.19,59 Examples are the introduction of different new antibiotics and the ultrasound to monitor the fetus. But also several associations between, for example, certain foods, smoking and infectious diseases (besides infections of the urinary tract) and adverse pregnancy outcomes were demonstrated. Subsequently measures such as screening (GBS colonization) and counselling programmes (stop smoking-programmes) were introduced.5 New insights challenge the preconception that ASB in pregnant women is a disease of great importance associated with preterm birth. Recent studies suggest that ASB might be more an expression of commensalism than a disease.60 If this is the case, an ASB screening programme may not be effective to reduce the burden of preterm birth.

An association does not always represent a causal relationship; the association between ASB during pregnancy and preterm birth, established a long time ago, may have been confounded by other (yet) unidentified risk factors for preterm birth.

How can we explain the results of studies that have shown that treatment of ASB with antibiotics reduces the incidence of preterm birth compared to treatment with placebo?216,61 This finding seems to support the hypothesis that there is a direct association between colonization of the urinary tract and preterm birth. However preterm birth is thought to be the result of a combination of factors including several infectious diseases
and antibiotics may achieve this reduction in preterm birth rate, by indiscriminate reduction of bacterial colonization and/or infectious loads elsewhere in the body.\textsuperscript{3} For example, both maternal genital Chlamydia infection and vaginal GBS colonization are associated with preterm birth. Some of the antibiotics used for the treatment of ASB will also cure smouldering asymptomatic genital infection or heavy vaginal GBS colonization, thereby conceivably reducing the risk for preterm birth.\textsuperscript{62,63} Finally infections outside of the urogenital tract such as periodontal infections, which have been associated with preterm birth, may also be unintentionally treated with an antibiotic treatment initiated for ASB.\textsuperscript{64} Preterm birth is evidently an important health care problem, but in our opinion an ASB screening programme is not one of the magic bullets to prevent it. Several studies found associations between ASB and preterm birth, whether or not via symptomatic UTI, but so far the natural history remains unknown.\textsuperscript{55-57} In more than 50% of preterm birth no obvious risk factors were identified.\textsuperscript{65} Regarding associations and causal relations surrounding preterm birth and UTI we are possibly only aware of the tip of the iceberg. More experimental or laboratory research to identify causal pathways leading to preterm birth or cascades possibly activated via ASB is desirable. Maybe our current tests are not sensitive enough to detect ‘signals’ or ‘substances’ produced by certain bacteria in certain circumstances that lead to preterm delivery or other adverse events similar to the hypothesis that endotoxins and/or phospholipases influence the synthesis of prostaglandins.\textsuperscript{12}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{The condition} & & & \\
\textbf{The condition sought should be an important health problem} & & Not certain \\
\textbf{The natural history of the condition should be adequately understood} & & Not certain \\
\textbf{There should be recognisable latent or early symptomatic stage} & & Not certain \\
\hline
\textbf{The treatment and test} & & & \\
\textbf{There should be an accepted treatment for patients with recognized disease} & & Not certain \\
\textbf{There should be an agreed policy on whom to treat as patients} & & Not certain \\
\textbf{There should be a suitable test} & & Not certain \\
\textbf{The test should be acceptable to the population} & & Not certain \\
\textbf{Facilities for diagnosis and treatment should be available} & & Yes \\
\hline
\textbf{The costs} & & & \\
\textbf{The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole} & & Not certain \\
\hline
\textbf{The screening programme} & & & \\
\textbf{Case-finding should be a continuing process and not a “once and for all” project} & & Yes \\
\textbf{There should be a defined target population (revised)} & & Not certain \\
\textbf{There should be scientific evidence of screening programme effectiveness (revised)} & & No \\
\textbf{The overall benefits of screening should outweigh the harm (revised)} & & Not certain \\
\hline
\end{tabular}
\caption{Summarizing Wilson and Jungner criteria for ASB screening in pregnant women to prevent pyelonephritis or/and preterm birth}
\end{table}
According to the available evidence presented in relation to the Wilson and Jungner criteria, summarized in table 1, there is still too much uncertainty. Insight into the natural course of ASB during pregnancy is lacking, the borderline-group is large, test results ambiguous, the effectiveness of ASB treatment with antibiotics or any other treatment to prevent preterm birth not established and the possible harms of antibiotic use during pregnancy may be worse than the disease.

Firstly, we conclude that the evidence for the introduction of an ASB screening programme in the Netherlands is too limited. Secondly, the revealed uncertainties push for a rigorous audit of ASB screening and treatment policies currently in place in other countries to scrutinize if such a policy is still desirable.
TEN

References

11. Meads C. Screening for asymptomatic bacteriuria in pregnancy (version 2); External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). UK National Screening Committee 2011.
30. Haswell B, Sidaway ME, de Wardener HE. Follow-up of 164 patients with bacteriuria of
DISCUSSION

B streptococcal bacteriuria early in pregnancy


Hort Study. BMC Complement Altern Med

cy--the Norwegian Mother and Child Co

outcome after use of cranberry in pregnan

Heitmann K, Nordeng H, Holst L. Pregnancy

meta-analysis of randomized controlled trials. J

al. Nonantibiotic prophylaxis for recurrent uri

2008;180:1367-72


widmer M, Gülmezoglu AM, Mignini L, Rog


Petrov S. The economic consequences of preterm birth during the first 10 years of life. BJOG 2005;112:10-5.


65. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371:164-75.