

Asymptomatic bacteriuria in pregnancy - Is it still necessary to screen & treat?

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Abstract

Asymptomatic bacteriuria (ASB) in pregnancy occurs in 2–10% of pregnant women although higher frequencies have also been reported, up to 40%. Pregnant women are more prone to develop urinary tract infections (UTI) because of dilatation of the renal system and decreased peristalsis of the ureters and bladder facilitating bacterial colonisation and ascending infection in pregnancy.

Enterobacteriaceae comprise approximately the majority of urine isolates, of which *Escherichia coli* is the most common pathogen. A urine culture is considered the gold standard for diagnosing bacteriuria. The biggest challenge however is differentiating between significant (disease) and insignificant colonisation (not related to symptoms or adverse events) of the urinary tract. In addition, it is not clear which microorganisms are considered uropathogens and which are contaminants resulting in a wide range of reported incidences of ASB.

ASB when considered a latent stage and UTI as a symptomatic stage are both recognizable conditions that may be associated with an increased risk of adverse pregnancy outcomes. However, most 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) and not all women with ASB develop a UTI. In addition, the optimal timing of ASB screening remains unclear because ASB is often not a permanent stage and can dissolve spontaneously.

It has always been suggested that untreated ASB is an important risk factor for preterm birth, however when critically reviewing the literature, we found that currently there is no clear causal association between untreated ASB in pregnant women and preterm birth.

Recent studies showed that the incidence of antepartum pyelonephritis has decreased in developed countries with estimated incidences between 0.07% and 0.5%. This decrease is also notable in countries without a screen and treat program for ASB thereby questioning the effectiveness of current screening programs.

There is much debate about the best pharmacological and/or non-pharmacological treatment for ASB. There is no consensus or good quality evidence guiding clinicians in how to treat and how long to treat ASB in pregnancy.

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. Possibly another not yet identified recognizable latent or early stage for pyelonephritis and/or preterm birth is present.

We conclude that the current evidence does not justify a screening programme for asymptomatic bacteriuria to prevent preterm birth or pyelonephritis.

Keywords: asymptomatic, bacteriuria, pregnancy

Summary of recommendations

- The distinction between significant disease and insignificant colonisation of the urinary tract in pregnancy is not clear, neither is clear which microorganisms are considered uropathogens and which contaminants (GoR B).
- Causality between ASB in pregnancy and adverse pregnancy outcomes such as preterm birth, pyelonephritis and symptomatic UTI is not proven (GoR A).
- The treatment of ASB in pregnancy could lead to harmful effects such as increase in antibiotic resistance and possible adverse effects on the newborn (GoR B).
- Current evidence does not justify a screenings programme for asymptomatic bacteriuria to prevent adverse pregnancy outcomes (GoR B).

1 Introduction

The objective of this chapter is to elucidate why screening and treating of asymptomatic bacteriuria (ASB) in pregnancy is not desirable based on recent studies. The introduction of a screening and treating program of ASB is mainly based on outdated studies performed in the 70s and 80s, even before introduction of ultrasound for pregnancy dating. 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 and re-evaluation of screening programs is a delicate process weighing the desirable and undesirable consequences [1], [2].

2 Methods

A systematic literature search was performed for the last 10 years (2005–2015) in PubMed using the following key words: “asymptomatic urinary tract infection” and “bacteriuria”. We limited search results to clinical studies of pregnant women written in the English language. A total of 159 publications were found and subsequently screened by title and, when appropriate, abstract. Only one clinical trial was found comparing pregnant women with ASB who were treated with pregnant women with ASB who were not treated.

The information identified through the literature review was supplemented by other papers identified by the authors. The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using ICUD standards (for details see Preface).

3 Epidemiology

ASB in pregnancy occurs in 2–17% of pregnant women although higher frequencies have also been reported, up to 40% [3], [4], [5].

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 thereby facilitating bacterial colonisation and ascending infection in pregnancy [6].

Risk factors for bacteriuria in pregnancy include underlying genitourinary anatomic or functional defects, diabetes, sickle cell disease, and history of recurrent urinary tract infections. Multiparity and disadvantaged socioeconomic status are also significant risk factors as were fertility treatments [7], [8], [9].

Enterobacteriaceae comprise approximately 95% of urine isolates, of which *E. coli* is the most common pathogen [10].

4 Diagnosis

For a screening programme it is important that one agrees which women have to be considered as patients [1]. The distinction between significant (disease) and insignificant colonisation (not related with symptoms or adverse events) of the urinary tract is often not clear-cut.

A urine culture is considered the gold standard for diagnosing bacteriuria [11]. The biggest challenge related to the diagnosis of ASB (and UTI) is differentiating between true bacteriuria and contamination and especially during pregnancy also between ASB and symptomatic UTI [12].

The first question: Does 'true' bacteriuria exist and is it possible to distinguish 'true' bacteriuria from contamination? 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 [13]. These bacteria are often considered as non-pathogens, bacteria that do not cause infection or disease in that specific area. However when these bacteria are introduced in a different environment like the bladder (via the urethra) they can become pathogenic (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 [13].

The variety of definitions and diagnostic criteria used for ASB underscore that it is not clear whom to treat as patients and whom not. As mentioned earlier 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 [14], [15]. Some argue that two consecutive urine cultures are desirable but the interval between the two urine cultures is not clearly defined [16].

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% [4]. The most common organism associated with bacteriuria is *Escherichia coli*. Examples of microorganisms alternately defined as uropathogen are coagulase negative staphylococci (CNS) and *Acinetobacter* spp. [10], [13].

The second question: Is it possible to distinguish between ASB and symptomatic UTI during pregnancy? The difference between ASB and UTI is often based on symptoms. The difficulty is that 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 [11]. A more important difference is that ASB is considered to be colonization and UTI an infection. A consequence of infection may be symptoms for example inflammation of the bladder wall due to the presence of bacteria is associated with frequency. In clinical practice the presence of leukocytes in a urine samples is often investigated to underpin the UTI diagnosis. However pyuria is nonspecific and not always indicates infection [11], [13]. Summarizing it remains difficult to differentiate between contamination, colonization (ASB) and true infection (UTI).

5 Pathogenesis

5.1 Is ASB the latent or early symptomatic stage?

ASB when considered a latent stage and UTI as a 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 diseases; symptomatic lower UTI, pyelonephritis and/or preterm birth. Moreover the strength of the association between ASB and the different diseases, especially preterm birth, is questioned. [10], [17], [18], [19].

Besides, 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) [10], [17], [18], [19]. In an old study by Lawson and Miller they reported that only 19.1% of pregnant women who developed symptomatic UTI had bacteriuria on initial screening [18]. This was even lower in recent cohort study by Kazemier et al., in this study they found that of all women who suffered from a UTI only 12.7% suffered from either treated or untreated ASB [10].

Another key issue while discussing the value of this criterion is that ASB is not a permanent stage since ASB can dissolve spontaneously. A long-term follow-up study in non-pregnant patients with DM showed that incidence of UTI is slightly increased in women with DM and untreated ASB compared to those without [20]. 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 [21].

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 [22].

5.2 Timing of screening

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 [15]. Stenqvist et al. 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. This recommendation is based on possible 'number of bacteriuria-free gestational weeks gained by treatment' however also later in pregnancy women developed bacteriuria [23]. 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 [24]. Unfortunately 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.

6 Consequences of untreated ASB in pregnancy

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 [14], [15], [25]. Therefore during the past decades several attempts have been made to reduce preterm birth with the use of screening (& treatment) programs including for ASB [10], [14], [15]. The question remains if screening (& treatment) programs for ASB truly lead to reduced preterm birth rates without unwanted negative effects for both the mother and newborn.

For a screenings program to be effective it should prevent the identified condition and therefore needs to meet certain criteria [1]. One of the essential criteria is that the natural history of the condition, including development from latent to established disease should be adequately understood.

ASB was considered the pre-clinical and possibly also pre-pathological stage of symptomatic UTIs including pyelonephritis [14], [25]. However this is not a correct assumption, since not all women with ASB develop a UTI and not all women who develop UTI had ASB prior thereto.

6.1 Preterm birth

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 [12], [26], [27], [28], [29]. The consequences of not treating ASB on preterm birth are less well established [17].

A meta-analysis of 14 randomized or quasi-randomised control trials showed that treatment of ASB with antibiotics was associated with reduced incidence of low birthweight babies (RR 0.6, 95% CI 0.5 to 0.9) and preterm birth (before 37 weeks) (RR 0.3, 95% CI 0.1 to 0.6).⁷ However the found relative risk of preterm birth was based on only two studies with poor quality and one of the studies included only women with group B streptococcal bacteriuria. The authors concluded that the overall quality of the studies were poor [17].

Moreover most trials were performed more than 25 years ago, before the widespread use of the ultrasound to measure the duration of pregnancy, which could have led to misclassification of preterm birth [30].

The described meta-analysis did not include a recent multicentre prospective cohort study with an embedded RCT by Kazemier et al., which could have changed the conclusion. For this study 4,283 pregnant women were screened in the Netherlands where currently no ASB screening programme is in place. The prevalence of ASB was 5% (n=248). Forty women were randomly assigned to treatment with nitrofurantoin and 45 to placebo. The other 163 women with ASB did not receive any treatment. No differences was found in the proportion of women with pyelonephritis, preterm birth or both between women treated with nitrofurantoin and placebo-treated women (2.9% vs. 1.9% adjusted odds ratio (OR) 1.5, 95% CI 0.6–3.5) or untreated and placebo treated women (2.5% vs. 2.9%; risk difference –0.4, 95% CI –3.6 to 9.4). These results underscore that currently there is no known association between untreated ASB in pregnant women and preterm birth [10].

In a large prospectively studied cohort of 26,844 pregnancies performed in Wales, United Kingdom, bacteriuria was found to be significantly associated with preterm birth in the initial univariable analyses. However, after adjustments for medical factors, demographic and social factors, the relationship disappeared [31].

Concluding the recent study by Kazemier et al. reveals that earlier assumptions that ASB is associated with preterm birth needs to be reconsidered.

6.2 Pyelonephritis

Pyelonephritis was estimated to occur in 2% of pregnancies with a recurrence rate up to 23% within the same pregnancy or soon after birth [32], [33]. 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% [34], [35]. These recent studies concluded once more that antenatal pyelonephritis is associated with preterm birth (10.3%–20% vs. 7.8%–7.9%) [34], [35]. The reduced incidence of antepartum pyelonephritis may have various reasons including the introduction of ASB screening programmes and/or improved antenatal care. The previously mentioned meta-analysis showed that 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) 0.2, 95% CI 0.1 to 0.4) [17]. However the recent RCT by Kazemier et al. found a low absolute risk of pyelonephritis in both women with ASB including untreated (2.4%) and women without ASB (0.6%) [10].

7 Treatment options

7.1 Antibiotics

Currently the most common way to treat both 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 [11].

Although a Cochrane meta-analysis showed that antibiotic treatment of ASB compared to no treatment (placebo) reduced both the incidence of pyelonephritis (reduction varying between 1%–4% to 20–35%) and preterm birth [15], [17]. 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 [21], [22]. Moreover a recent study of Kazemier et al. showed that untreated ASB is associated with symptomatic UTI and pyelonephritis however not with preterm birth [10].

A present issue that may have an effect on antibiotic treatment of ASB and prevention of other infectious diseases is the increasing prevalence of antimicrobial resistance [36]. Screening for ASB and subsequent treatment with antibiotics may cause an increase of the use of antibiotics, especially if the number needing treatment needed to treat is high. This again may subsequently undermine the effectiveness of a screening programme because one of the main causes of antimicrobial resistance is the overuse of antibiotics.

Emerging evidence showing possible long-term consequences of antibiotic use in pregnant women are reason for concern [37], [38], [39]. 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 [37], [38], [39]. Also maternal exposure to certain antibiotics is associated with childhood asthma and childhood obesity by 7 years of age [40], [41]. Significant alterations in overall microbiota community structure, as well as a reduction in microbiota richness and a depletion of *Bacteroides* has been noted after intrapartum antibiotic prophylaxis [42].

Moreover antibiotics may cause several side-effects such as gastro-intestinal symptoms and vaginal candidiasis [43], [44]. 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.

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 [45]. 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 four to 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 [46].

7.2 Non-pharmacological treatment

Many other interventions have been proposed to treat bacteriuria besides antibiotics such as cranberry products, probiotics and behavioural interventions [43].

One of the possible non-pharmacological interventions are cranberry products [47]. 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 0.5, 95% CI 0.3-0.8) [47]. A pilot study found a good compliance and tolerability of cranberry capsule ingestion also during pregnancy [48] and currently a Cochrane review is being performed to determine the role of cranberries in the treatment of ASB in pregnant women [49]. However this study is not needed when ASB screening and treatment is not considered worthwhile. A recent study investigated the safety of cranberry product use during pregnancy using the Norwegian Mother and Child cohort including almost 70,000 pregnancies. No increased risk for malformations and other adverse pregnancy outcomes were observed [50]. Nevertheless, in this same study an association was found between the use of cranberry in late pregnancy and vaginal bleeding after pregnancy week 17, which should be investigated in appropriate clinical studies more carefully.

8 The costs of screening

Preterm birth is extremely costly due to increased maternal and neonatal admissions [51]. Therefore screening and treatment of ASB in pregnant women would prevent preterm birth it will almost always outweigh the costs of a ASB screening programme even with a high number of patients to treat since. Studies showed that the cumulative costs for children born preterm during the first 10 years of life doubled or more compared those who are born term [51], [52].

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% or higher [53].

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.

9 Conclusions

New insights challenge the preconception that ASB in pregnant women is a disease of great importance associated with preterm birth [10]. Recent studies suggest that ASB might be more an expression of commensalism than a disease [54]. 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.

The question remains 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 [27], [55]? 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 [25], [56], [57].

In addition, even though antibiotic treatment of ASB seems to decrease the risk of pyelonephritis during pregnancy, the majority of women with pyelonephritis were screened negative for ASB. Furthermore, recent studies showed that the overall risk of pyelonephritis is small, which questions the need for a screening program even further.

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 or pyelonephritis not established and the possible harms of antibiotic use during pregnancy may be worse than the disease.

We conclude that the current evidence does not justify a screenings programme for ASB to prevent preterm birth or pyelonephritis.

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