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CHAPTER 9

Maternal and neonatal consequences of untreated asymptomatic bacteriuria in pregnancy, a prospective cohort study

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ABSTRACT

Background

Many countries routinely apply a screen-treat policy for asymptomatic bacteriuria (ASB) in pregnancy. However, such a policy is based on trials performed more than 30 years ago. As recent research has focused more on possible neonatal adverse effects of antibiotics in pregnancy, we re-evaluated the consequences of untreated ASB in pregnancy.

Methods

In a multicentre cohort study we screened women with a singleton pregnancy between 16 and 22 weeks of gestation for ASB using a urine dipslide, and compared untreated ASB-positive and ASB-negative women. We used multivariable logistic regression after adjustment for potential confounders. Primary outcome was a composite of pyelonephritis and/or preterm birth <34 weeks. Secondary outcomes were preterm birth <37 weeks and neonates being small for gestational age (< 10^{th} percentile).

Findings

Our study group comprised 4,018 ASB-negative and 163 untreated ASB-positive women. The proportion of women with pyelonephritis and/or preterm birth did not significantly differ between untreated ASB-positive and ASB-negative women (3.1% versus 1.9%, adjOR 1.6, 95%CI 0.62 to 3.9). Untreated ASB-positive women developed pyelonephritis in 2.5% of cases, compared to 0.60% in ASB-negative women (adjOR 3.8, 95%CI 1.3 to 11). The proportion of preterm deliveries <34 weeks (1.2 versus 1.3, adjOR 0.90, 95%CI 0.22 to 3.7), preterm deliveries <37 weeks (5.5% versus 5.2%, adjOR 1.1, 95%CI 0.54 to 2.1) and the number of small for gestational age neonates (8.6% versus 8.6%, adjOR 0.90, 95%CI 0.51 to 1.6) did not differ.

Interpretation

In women with an uncomplicated singleton pregnancy, the presence of ASB between 16 and 22 weeks of gestation is neither associated with preterm birth nor with growth restriction. There was a significant association with pyelonephritis, though the absolute risk of pyelonephritis in ASB is very low. These data question a routine screen-treat policy for ASB in low risk women with a singleton pregnancy.

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INTRODUCTION

Asymptomatic bacteriuria (ASB) is defined as the isolation of bacteria in at least 10e5 colony forming units (CFU)/mL of cultured urine, in the absence of signs or symptoms of a urinary tract infection (UTI). ASB is found in 2% to 10% of pregnant women[1;2]. Untreated ASB in pregnancy is thought to be responsible for serious complications in mother and child, such as pyelonephritis, preterm birth, and low birth weight. A Cochrane review showed that treatment with antibiotics was effective in reducing the incidence of pyelonephritis, from 21% in untreated women to 5% in treated women (RR 0.23, 95%CI 0.13-0.41). Similar positive effects were observed for birth weight below 2500g: 8.5% versus 13% (RR 0.66, 95%CI 0.49-0.89), and for preterm delivery, defined as a gestational age <38 weeks, though not statistically significant: 13% versus 21% (OR 0.37, 95%CI 0.10-1.4)[3]. However, trials in this review were performed more than 30 years ago. These studies had several methodological shortcomings, such as a lack of adequate concealment of allocation, incomplete description of research methods, and inconsistencies in definitions of outcomes[3]. Despite these shortcomings, routine screening and treatment of ASB in pregnancy is applied in many countries[1;4-6].

It is possible that changes in antenatal care, such as the introduction of ultrasound for pregnancy dating, have influenced the clinical course or incidence of complications of untreated ASB. In addition, awareness of possible adverse effects of maternal antibiotics on the neonate has grown[7;8], especially after publication of the long term follow up of the ORACLE II study[9]. This trial indicated an increased risk of cerebral palsy in neonates whose mothers received antibiotics for threatened preterm labour. Overall, antibiotics use is increasingly recognized as a factor that drives antibiotic resistance[10].

The combination of the low grade of evidence underpinning ASB screening in pregnancy, the possible negative effects of antibiotics to treat ASB, and the fact that in the Netherlands routine screening for ASB in pregnancy was not applied at the start of our study[11] motivated our research. Our objective was to assess maternal and neonatal consequences of untreated ASB in pregnancy in a national prospective cohort study, in order to re-evaluate the rationale and effectiveness of a screen-and-treat strategy.

METHODS

Study design

Between October 2011 and August 2013, we performed a multicentre cohort study with an embedded double-blind placebo-controlled trial in 8 hospitals and 5 ultrasound centres in the Netherlands. Follow-up was completed in August 2014. The study was approved by the research ethics committee of the Academic Medical Centre, Amsterdam, the Netherlands (MEC 2011-073) and by the institutional review board of each participating hospital. The full study protocol is reported elsewhere [12]. Results of the embedded randomized controlled trial will be reported separately.

Participants

Women with a singleton pregnancy without symptoms of a UTI between 16 and 22 weeks of pregnancy were eligible. We offered these women screening for ASB, which was not routinely available outside our study. Women with a history of preterm delivery before 34 weeks, signs of threatening preterm delivery, foetal congenital malformations, antibiotic use within two weeks of

screening, known G6PD deficiency, hypersensitivity to nitrofurantoin, or risk factors for complicated UTI, such as pre-gestational diabetes mellitus, use of immunosuppressive medication, functional or structural abnormalities of the urinary tract were excluded.

Procedures

A single dipslide (UricultW, Orion Diagnostica) with two media (cysteine lactose electrolyte deficient (CLED) medium and MacConkey medium) was used to detect ASB. The dipslide has a 98.0% sensitivity and 99.6% specificity in detecting ASB in pregnancy and was shown to be a good alternative for ordinary culture[13].

Dipslides were considered positive when the colony concentration was ≥ 10e5 CFU/mL of a single microorganism or when two different colony types were present but one had a concentration of ≥10e5 CFU/mL. When more than two species were present, the urine was considered contaminated. In our study protocol[12] we described that Group B *Streptococcus* (GBS) in lower colony counts would also be considered ASB. However, during the recruitment phase of our study, Hooton *et al.* published a paper in the New England Journal of Medicine[14] that showed that the positive predictive value of true GBS bacteriuria in midstream cultures was very low, even at higher colony counts. We therefore decided not to consider women with a GBS colony count below 10e5 CFU/mL ASB-positive.

Since nitrofurantoin is the first choice antibiotic in treatment of uncomplicated UTI in the Netherlands [11;15], we tested sensitivity to nitrofurantoin in microorganisms found. More detailed information about these procedures can be found elsewhere[12]. All women with ASB, defined as a positive dipslide without the presence of symptoms of a urinary tract infection, were invited to participate in a randomized placebo-controlled trial to assess the effectiveness of treatment with nitrofurantoin. To maintain blinding for bacteriuria status, some ASB-negative women were also offered trial participation; when they accepted, these women received placebo. The majority of women did not want to participate and did not receive treatment. This paper contains the outcomes of the untreated ASB-positive women and the ASB-negative women. The outcomes of the women in the trial (nitrofurantoin treated and placebo treated) will be reported separately.

Study outcomes

The primary outcome was a composite of pyelonephritis and/or delivery before 34 weeks of gestation. Pyelonephritis was defined as hospital admission with at least two of the following features: fever (at least 38.0°C), symptoms of pyelonephritis (nausea, vomiting, chills, costo-vertebral tenderness) and a positive urine culture. Secondary outcomes were adverse neonatal outcome, death before discharge from the nursery or severe morbidity.

A composite measure of severe neonatal morbidity was defined as presence of one or more of the following: severe respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), periventricular leucomalacia > grade 1, intracerebral haemorrhage > grade II, necrotizing enterocolitis (NEC) > stage 1 or proven sepsis (including GBS sepsis).

Other outcome parameters were neonatal weight, time to delivery, (spontaneous) preterm birth before 32 and 37 weeks, admission to neonatal intensive care unit and maternal morbidity including UTI. We defined UTI as a clinical report of a urinary tract infection which was treated with antibiotics. Since most women in the Netherlands go to their general practitioner in case of UTI symptoms, culture information was not available.

In all cohort participants data on outcomes were recorded via questionnaires, completed by the participants, and data provided by the hospitals and midwives up to 6 weeks after delivery. Data on participating women were also linked to the Perinatal Registry Netherlands (PRN), based on women's date of birth, expected due date, and postal code. The PRN is a population-based database containing information on 96% of all pregnancies, deliveries and (re)admissions until 28 days after birth. Data are obtained by a validated linkage procedure between the midwifery registry, the obstetrics registry, and the neonatology registry [16;17]. The PRN approved the use of their database for the purpose of this study (approval number 13.64).

Sample size calculation and study monitoring

Based on the available literature[3] the proportion of women with a primary outcome was hypothesized to be 10% in the treatment and 25% in the no treatment group. The power analysis required 110 women per group (two-sided test) to demonstrate this difference with 80% power and a 5% type one error probability. Based on this, we anticipated to screen 4,400 women

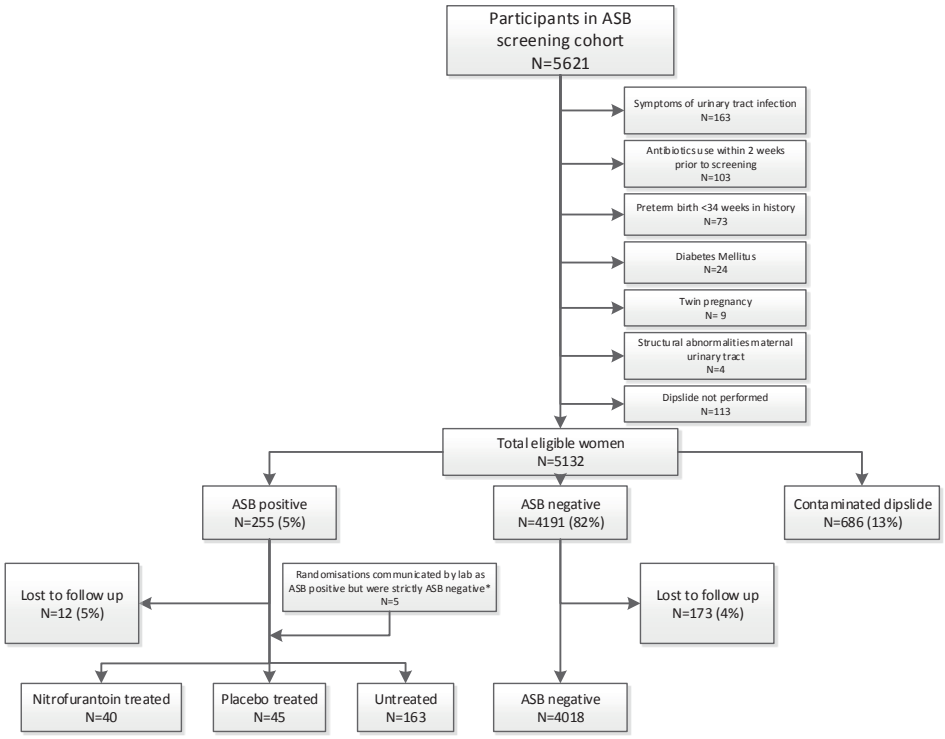
An independent data and safety monitoring committee monitored the trial. At the planned interim analysis, conducted when outcome data were available for 66 participants in the trial (30% of the planned sample), the data revealed that the primary outcome occurred much less frequent in both the intervention as the placebo group than anticipated. To increase the certainty of these findings, the primary outcome data of the women from the cohort were also reviewed (outcome available for 50 untreated ASB-positive women and 1,863 ASB-negative women). These data confirmed the low incidence of the primary outcome (1.8% in the untreated ASB-positive and 1.7% in the ASB-negative women) due to low incidence of pyelonephritis. With this information, we would have to randomize at least 1900 women with ASB to show that treatment would reduce the incidence of pyelonephritis from 1.8% (prevalence in the untreated ASB-positive women) to 0.5% (prevalence in the ASB-negative women (alpha-error 5%, 80% power). Based on these data, enrolment in the randomized controlled trial and the cohort study was halted on the 10th of June, 2013.

Statistical analysis

Baseline characteristics of the cohort were compared between untreated ASB-positive and ASB-negative women with Student's t test, Mann-Whitney U test or Chi-square statistic where appropriate. In case of missing values, multiple imputation (ten times) was used to obtain complete data without loss of power[18]. Both patient characteristics and outcomes were taken into account to impute missing data[19]. The difference in the proportion of primary and secondary outcomes between ASB-positive and ASB-negative women was expressed as an odds ratio, with 95% confidence intervals, adjusted for potential confounders such as smoking, low education, conception through in vitro fertilization or intra cytoplasmic sperm injection and pre-existent hypertension. A Kaplan-Meier curve was constructed to analyse time from screening to delivery. The curves for ASB-positives and ASB-negatives were compared using the log rank test. P-values below 0.05 were considered to indicate statistical significance. Analyses were performed using IBM SPSS Statistics (version 20.0, IBM Corp).

RESULTS

A total of 5,621 women were included in the study cohort, of whom 4,412 (78%) in ultrasound centres and 1,209 (22%) in hospitals. Of the 5,132 eligible women, 255 (5%) were ASB-positive. These women were invited to participate in the randomized controlled trial, and 85 consented: 40 women were allocated to nitrofurantoin and 45 to placebo. The large majority of ASB-positive women, n=241 (95%) did not want to receive antibiotics in pregnancy for an asymptomatic condition. Outcomes were available for 95% of the ASB-positive women and 95% of ASB-negative women. In the final analysis, we could include data of 4,018 ASB-negative women and 163 untreated ASB-positive women (figure 1).



* one 10e5 yeast, three 10e4 uropathogen, one contaminated (4 in Nitrofurantion group, 1 in placebo group)

Figure 1 | Flowchart of participants

Baseline characteristics

Mean maternal age was 31 years. Mean pre-pregnancy Body Mass Index was 23.5, both in the untreated ASB-positive women and in ASB-negative women. Untreated ASB-positive women were significantly more often smokers than ASB-negative women (12% versus 5.7%, p=0.002, table 1). Table 2 shows the microorganisms found in the untreated ASB-positive women and their sensitivity to nitrofurantoin. Overall, the majority of microorganisms were sensitive to nitrofurantoin (91%, table 2). None of the women carried GBS in 10e5 CFU/mL or more. Some participants had missing variables for gestational age at birth (44; 1.0%), pyelonephritis (71; 1.7%) and neonatal birth weight (65; 1.5%).

Table 1 | Baseline characteristics of the cohort

Characteristic	untreated ASB-positive N=163	ASB-negative N=4018	*P*-value
Maternal age, mean (SE)	31 (0.38)	31 (0.07)	0.14
Body Mass index, mean (SE)	23.5 (0.31)	23.5 (0.06)	0.88
Non-Caucasian, N (%)	30 (18)	651 (16)	0.45
Low education, N (%)	18 (11)	295 (7.3)	0.07
Nulliparous, N (%)	69 (42)	1653 (41)	0.75
Smoking, N (%)	20 (12)	230 (5.7)	0.002
Alcohol, N (%)	2 (1.2)	57 (1.4)	0.86
Pre-existent hypertension, N (%)	1 (0.61)	40 (1.0)	0.63
Pregnancy after fertility treatment , N (%)	6 (3.7)	105 (2.6)	0.45
Gestational age at screening, mean, (SE)	20+0 (0.54)	20+0 (0.10)	0.50

Table 2 | Microorganisms and sensitivity to nitrofurantoin

	Total		Nitrofurantoin sensitivity*		
Microorganism	**N**	**%**	**Sensitive**	**Intermediate**	**Resistant**
Escherichia Coli	108	66.3	108 (100)		0
Staphyloccus spp[$]	15	9.2	15 (100)	0	0
Enterococcus spp	16	9.8	16 (100)	0	0
Klebsiella spp	6	3.7	4 (67)	0	2 (33)
Citrobacter spp	4	2.5	4 (100)	0	0
Proteus spp	5	3.1	0	0	5 (100)
Enterobacter spp	3	1.8	1 (33)	1 (33)	1 (33)
Acinetobacter spp	2	1.2	0	0	2 (100)
Other	4	2.5	1 (25)	0	3 (75)
Total	163		149 (91.4)	1 (0.6)	13 (8.0)

* Sensitivity expressed in N (%)

$ spp = species

Primary outcome

The proportion of women which developed pyelonephritis and/or preterm birth <34 weeks did not differ significantly between untreated ASB-positive women and ASB-negative women: 3.1% versus 1.9%, adj OR 1.6, 95%CI 0.62-3.9). Untreated ASB-positive women developed more often pyelonephritis: 2.5% versus 0.60%, (adj OR 3.8, 95%CI 1.3-11, table 3). Of the 28 women diagnosed with acute pyelonephritis, four women (14%) had ASB between 16 and 22 weeks. Median admission for women with pyelonephritis was 3 days (range 2-10 days). The course of disease in these women was mild, none needed admission to an intensive care unit.

Maternal outcomes cohort

Untreated ASB-positive women developed more often a symptomatic UTI compared to ASB-negative women: 21% versus 7.9% (adj OR 3.0 95%CI 2.0-4.4). Untreated ASB-positive women also had more often a recurrent UTI: 10% versus 2.6% (adj OR 4.2, 95%CI 2.2-8.1). The proportion of women who developed pregnancy induced hypertension did not significantly differ between untreated ASB-positive and ASB-negative women (5.5% versus 5.9%, adj OR 0.93, 95%CI 0.47-1.9). The same applied to gestational diabetes: 1.8% versus 2.8% (adj OR 0.67, 95%CI 0.21-2.2, table 3).

Neonatal outcomes cohort

The median gestational age at delivery did not significantly differ between women with untreated ASB- and ASB-negative women: 39+4 weeks versus 39+4 weeks (p=0.71). There were no significant differences either in preterm deliveries before 37 weeks (5.5% versus 5.2%; adj OR 1.1, 95%CI 0.54-2.1) or before 32 weeks (0.61% versus 0.90%, adj OR 0.70, 95%CI 0.10-5.1).

The chances of delivery after screening was expressed using Kaplan-Meier curves (figure 2). Time to delivery did not significantly differ between untreated ASB-positive women and ASB-negative women (logrank Test, p=0.84). In addition, the proportion of neonates small for gestational age below the 10th percentile did not differ between untreated ASB-positive women and ASB-negative women: 8.6 versus 8.6% (adj OR 0.90, 95%CI 0.51-1.6). The proportion of perinatal deaths was 1.2 versus 0.55 (adj OR 2.3 95%CI 0.53-9.8). The composite severe neonatal morbidity was observed in 0.61 versus 0.97% (adj OR 0.65, 95% CI 0.24-1.8, table 3).

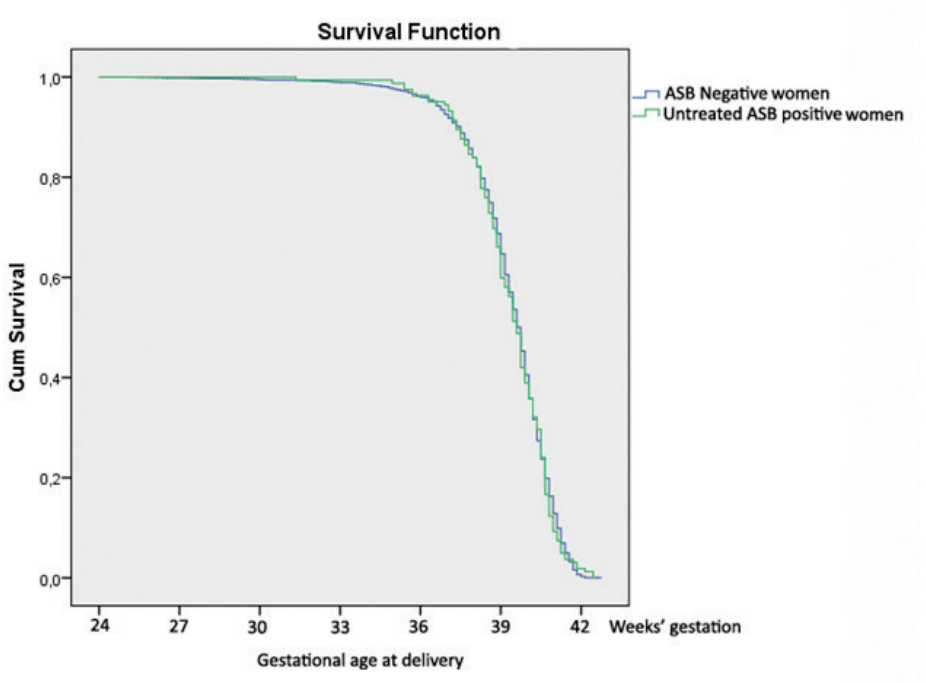


Figure 2 | Time to delivery from screening for untreated ASB-positive women and ASB-negative women.

Table 3 | Maternal and neonatal outcomes.

	untreated ASB-positive N=163[&]	ASB-negative N=4018[&]	Adjusted [$] OR	95% CI
Primary outcomes				
Composite primary outcome	5 (3.1)[#]	77 (1.9)[#]	1.6	0.62-3.9
Pyelonephritis	4 (2.5)	24 (0.60)	3.8	1.3-11
Delivery <34 weeks	2 (1.2)	54 (1.3)	0.90	0.22-3.7
Maternal outcomes				
Urinary tract infection treated with antibiotics during pregnancy	34 (21)	317 (7.9)	3.0	2.0-4.4
Recurrent urinary tract infection treated with antibiotics during pregnancy	17 (10)	105 (2.6)	4.2	2.2-8.1
Urinary tract infection treated with antibiotics postpartum (within 6 weeks)	11 (6.7)	165 (4.1)	1.7	0.86-3.3
Antibiotics during pregnancy other than for UTI	9 (5.5)	167 (4.2)	1.4	0.68-2.7
Gestational diabetes	3 (1.8)	113 (2.8)	0.67	0.21-2.2
Pregnancy induced hypertension	9 (5.5)	237 (5.9)	0.93	0.47-1.9
Pre-eclampsia	2 (1.2)	105 (2.6)	0.52	0.13-2.2
HELLP	0 (0)	24 (0.60)	NA	NA
Kidney stones	2 (1.2)	15 (0.37)	2.8	0.59-13
Cholestasis	3 (1.8)	20 (0.50)	4.0	1.2-14
Thrombo-embolic events	0 (0)	8 (0.20)	NA	NA
Non-spontaneous onset of labour	49 (30)	963 (24)	1.3	0.90-1.9
Epidural/spinal analgesia during labour	43 (26)	985 (25)	1.1	0.76-1.6
Endometritis (within 6 weeks of delivery)	0 (0)	16 (0.40)	NA	NA
Mastitis (within 6 weeks of delivery)	0 (0)	11 (0.27)	NA	NA
Neonatal outcomes				
Male foetus	59 (36)	2057 (51)	0.55	0.40-0.76
Gestational age at delivery, median	39+4	39+4		
Preterm birth <37 weeks	9 (5.5)	207 (5.2)	1.1	0.54-2.1
Preterm birth <32 weeks	1 (0.61)	36 (0.90)	0.70	0.10-5.1
Preterm birth <28 weeks	1 (0.61)	19 (0.47)	1.4	0.19-11
Birthweight, mean (SE)	3425 (45)	3454 (9.0)		
SGA <P10	14 (8.6)	346 (8.6)	0.90	0.51-1.6
SGA<P5	7 (4.3)	168 (4.2)	0.89	0.41-2.0
Perinatal death	2 (1.2)	22 (0.55)	2.3	0.53-9.8
Composite severe morbidity*	1 (0.61)	39 (0.97)	0.65	0.24-1.8
Admission to a Neonatal Intensive Care Unit	5 (3.1)	175 (4.3)	0.49	0.10-2.5
Neonatal sepsis confirmed with culture	0 (0)	25 (0.62)	NA	NA
Congenital abnormalities	1 (0.61)	39 (0.97)	0.65	0.09-4.8

& expressed as N (%) unless indicated otherwise

2 women had a pyelonephritis as well as a preterm delivery before 34 weeks

* Respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, bronchopulmonary disease, sepsis

$ Odds ratios were adjusted for: smoking, low education, conception through in vitro fertilization or intra cytoplasmic sperm injection and pre-existent hypertension

DISCUSSION

This study shows that women with untreated ASB, although at increased risk of pyelonephritis and symptomatic UTI during pregnancy, face a limited absolute risk of pyelonephritis (2.5%), which is much lower than previously reported in the literature[4]. These women are not at increased risk of preterm birth, nor are they expected to give more often birth to a small for gestational age infant.

The study reported here is one of the largest prospective cohorts of women with ASB of the last 30 years. Since the Netherlands was one of the few countries that had not adopted a routine ASB screen and treat policy, we were able to study the natural course of untreated ASB. Our study group is comparable to the general population of women with a singleton pregnancy without diabetes mellitus or prior preterm birth. Women were enrolled from across the Netherlands in 13 different centres, geographically spread, with different levels of obstetric care and diverse socio-economic status. Most pregnant women in the Netherlands receive initial antenatal care from a midwife[20], and get a 20 weeks anomaly scan at an ultrasound centre. The majority of our study group was recruited during their visit to an ultrasound centre. The frequency of preterm birth in this study was consistent with the frequency of preterm birth in singleton pregnancies in the Netherlands[21] underscoring the generalizability of our results.

Our study has some potential limitations. The number of untreated ASB women was relatively small (n=163). Women reported themselves whether they had had a symptomatic UTI treated with antibiotics or not. Since midwifes in The Netherlands are not allowed to prescribe antibiotics, most pregnant women with complaints of a UTI were treated by their general practitioner[22], and prescription of such UTI antibiotics is not typically recorded in hospital records. The rate of symptomatic UTI in the untreated ASB-positive group could have been influenced by the invitation to participate in the RCT, making the participants more aware to UTI symptoms. However, the clear association between ASB on one hand and UTI and pyelonephritis on the other hand indicates that our procedures to detect ASB and subsequent disease were adequate.

The optimal gestational age to screen for ASB is a topic of discussion. We screened women between 16 and 22 weeks of gestation. A previous study showed that screening before 20 weeks may miss more than half of women with ASB[23]. In contrast, another study showed that 1 in 5 cases of acute pyelonephritis occurred in the first trimester[24]. Timing of screening could have influenced our findings, which implies that we may have missed some cases of acute pyelonephritis before screening.

Hill *et al*. reported an incidence of antepartum acute pyelonephritis of 14 per 1,000 deliveries[24]. In the recent studies of Wing *et al*.[25]and Farkash *et al*. [26] comparably low numbers of women were hospitalized for acute pyelonephritis, namely 0.5% and 0.07% respectively. In contrast, older studies have reported much higher rates of pyelonephritis in untreated women during pregnancy, up to 21%[3]. The contrasting results may be due to differences in diagnostic criteria, antenatal care, behavioural changes, comorbidities, or microbial factors over the years[27]. Other possible reasons for the discrepancies are differences between the screened populations. The present study excluded women with diabetes mellitus, structural abnormalities of the urinary tract and women with a previous preterm birth, as we focused on an otherwise low-risk population of women.

In the Netherlands, health care is accessible for everyone and most pregnant women with complaints of a UTI go to their general practitioner (GP) [22]. This good accessibility of GPs may account for the relatively low rate of pyelonephritis. As women contact their GP with early symptoms of a UTI, as advised by their midwives, this might prevent progression to pyelonephritis.

Associations between ASB and preterm birth and low birth weight have all been reported in literature[3] before the introduction of ultrasound for dating pregnancies. In addition, in most of the older studies preterm birth was defined as below 38 weeks instead of the current cut off of 37 weeks. This could explain the absence of an association between ASB and preterm birth.

A major issue is whether the natural course of ASB these days still warrants treatment, and whether the prevalence of complications justifies screening. The results of this study are relevant in view of possible adverse effects of maternal antibiotics on the neonate [7;8]. The 7-year follow up of the ORACLE II trial showed an increased risk of cerebral palsy in neonates whose mother received antibiotics during pregnancy[9]. Furthermore, antibiotic use is correlated with emerging antibiotic resistance[10;28;29]. A routine screen and treat program in the Netherlands could mean that 5% of all pregnant women and their unborn children receive antibiotics around 20 weeks of gestation, without a trivial gain in health outcome. Although we found a higher risk of UTI in women with untreated ASB, it suffices to treat UTI as ASB would be treated. A substantial number of women treated for ASB do not benefit from treatment and thus are unnecessarily exposed to the possible side effects of antibiotics.

Final conclusion

In our study, we found no association between ASB in midtrimester pregnancy and preterm birth or growth restriction. Although there was an association between ASB and pyelonephritis, the absolute risk of pyelonephritis after ASB was low and the majority of women with pyelonephritis did not have ASB. Our data question a routine policy of midtrimester screening and subsequent treatment for ASB in low risk women with a singleton pregnancy.

REFERENCES

1. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis 2005; 40(5):643-654.
2. Guinto VT, De GB, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2010;(9):CD007855.
3. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2007;(2):CD000490.
4. Australian Government Department of Health and Ageing. Clinical Practice Guidelines: Antenatal Care – Module 1. 2-4-2013. Commonwealth of Australia.
5. Lin K, Fajardo K. Screening for asymptomatic bacteriuria in adults: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2008; 149(1):W20-W24.
6. National Collaborating Centre for Women's and Children's Health. NICE clinical guideline 62; Antenatal care: routine care for the healthy pregnant woman. 2008.
7. Miller JE, Pedersen LH, Sun Y, Olsen J. Maternal use of cystitis medication and childhood epilepsy in a danish population-based cohort. Paediatr Perinat Epidemiol 2012; 26(6):589-595.
8. Wright AJ, Unger S, Coleman BL, Lam PP, McGeer AJ. Maternal antibiotic exposure and risk of antibiotic resistance in neonatal early-onset sepsis: a case-cohort study. Pediatr Infect Dis J 2012; 31(11):1206-1208.
9. Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet 2008; 372(9646):1319-1327.
10. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365(9459):579-587.
11. Nederlandse Vereniging voor Obstetrie en Gynaecologie. NVOG Guideline: urineweginfectie in de zwangerschap. 2011.
12. Kazemier BM, Schneeberger C, De ME, Van WA, Bossuyt PM, Vogelvang TE et al. Costs and effects of screening and treating low risk women with a singleton pregnancy for asymptomatic bacteriuria, the ASB study. BMC Pregnancy Childbirth 2012; 12:52.
13. Mignini L, Carroli G, Abalos E, Widmer M, Amigot S, Nardin JM et al. Accuracy of diagnostic tests to detect asymptomatic bacteriuria during pregnancy. Obstet Gynecol 2009; 113(2 Pt 1):346-352.
14. Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. N Engl J Med 2013; 369(20):1883-1891.
15. Van Haaren KAM VHVVSTAYRGSTRGVPB. NHG-standaard Urineweginfectie (Tweede herziening). 8[Huisarts Wet], 341-352.
16. Meray N, Reitsma JB, Ravelli AC, Bonsel GJ. Probabilistic record linkage is a valid and transparent tool to combine databases without a patient identification number. J Clin Epidemiol 2007; 60(9):883-891.

17. Tromp M, Ravelli AC, Meray N, Reitsma JB, Bonsel GJ. An efficient validation method of probabilistic record linkage including readmissions and twins. Methods Inf Med 2008; 47(4):356-363.
18. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006; 59(10):1087-1091.
19. Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006; 59(10):1092-1101.
20. Scholmerich VL, Posthumus AG, Ghorashi H, Waelput AJ, Groenewegen P, Denktas S. Improving interprofessional coordination in Dutch midwifery and obstetrics: a qualitative study. BMC Pregnancy Childbirth 2014; 14:145.
21. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Trends in preterm birth: singleton and multiple pregnancies in the Netherlands, 2000-2007. BJOG 2011; 118(10):1196-1204.
22. Feijen-de Jong EI, Baarveld F, Jansen DE, Ursum J, Reijneveld SA, Schellevis FG. Do pregnant women contact their general practitioner? A register-based comparison of healthcare utilisation of pregnant and non-pregnant women in general practice. BMC Fam Pract 2013; 14:10.
23. McIsaac W, Carroll JC, Biringer A, Bernstein P, Lyons E, Low DE et al. Screening for asymptomatic bacteriuria in pregnancy. J Obstet Gynaecol Can 2005; 27(1):20-24.
24. Hill JB, Sheffield JS, Mcintire DD, Wendel GD, Jr. Acute pyelonephritis in pregnancy. Obstet Gynecol 2005; 105(1):18-23.
25. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. Am J Obstet Gynecol 2014; 210(3):219-6.
26. Farkash E, Weintraub AY, Sergienko R, Wiznitzer A, Zlotnik A, Sheiner E. Acute antepartum pyelonephritis in pregnancy: a critical analysis of risk factors and outcomes. Eur J Obstet Gynecol Reprod Biol 2012; 162(1):24-27.
27. Ki M, Park T, Choi B, Foxman B. The epidemiology of acute pyelonephritis in South Korea, 1997-1999. Am J Epidemiol 2004; 160(10):985-993.
28. Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother 2003; 51(1):69-76.
29. Rizvi M, Khan F, Shukla I, Malik A, Shaheen. Rising prevalence of antimicrobial resistance in urinary tract infections during pregnancy: necessity for exploring newer treatment options. J Lab Physicians 2011; 3(2):98-103.