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CHAPTER 6

Asymptomatic bacteriuria and urinary tract infections in special patient groups: women with diabetes mellitus and pregnant women

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ABSTRACT

Purpose of review

Asymptomatic bacteriuria (ASB) and urinary tract infections (UTIs) in women with diabetes mellitus and during pregnancy are common and can have far-reaching consequences for the woman and neonate. This review describes epidemiology, risk factors, complications and treatment of UTI and ASB according to recent developments in these two groups.

Recent findings

Most papers addressing the epidemiology and risk factors of ASB and UTI in diabetic and pregnant women confirmed existing knowledge. New insights were obtained in the association between sodium-glucose cotransporter-2 (SGLT2) inhibitors, as medication for diabetes mellitus type 2, and a small increased risk for UTI due to glucosuria and the possible negative effects of UTI, including urosepsis, on bladder and kidney function in diabetic women. Predominantly, potential long-term effects of antibiotic treatment of ASB or UTI during pregnancy on the neonate have received attention, including antibiotic resistance and epilepsy.

Summary

SGLT2 inhibitors were associated with a small increased risk for UTI, UTI in diabetic women may lead to bladder and kidney dysfunction, and antibiotic treatment of ASB and UTI during pregnancy was associated with long-term effects on the neonate. Up-to-date research on the effectiveness and long-term effects of ASB screening and treating policies, including GBS bacteriuria in pregnancy, is warranted to inform clinical practice.

INTRODUCTION

Asymptomatic bacteriuria (ASB) and urinary tract infection (UTI) are among the most common diagnoses worldwide. Particularly in special patient groups such as women with diabetes mellitus and pregnant women, complications can have far-reaching consequences such as pyelonephritis or adverse effects for the neonate. Moreover, UTIs may present differently in diabetic and pregnant women owing to disparities in underlying pathogenesis or causative uropathogens. This review provides an overview of the most recent clinical studies of interest (published from 2012 till now) concerning epidemiology, risk factors, consequences and treatment of UTI and ASB in diabetic and pregnant women.

Asymptomatic bacteriuria and urinary tract infection in women with diabetes mellitus

Women with diabetes mellitus are considered susceptible to both UTI and some of its rare but severe consequences.

Epidemiology

No recent studies have been published on the prevalence of ASB in women with diabetes mellitus. The prevalence of ASB is known to be higher in women with diabetes mellitus compared to those without diabetes mellitus (1).

A study using general practice data from the years 1990-2007 in the United Kingdom confirmed previously described increased adjusted hazard ratio of UTI of 1.53 (95% confidence interval (CI) 1.45-1.60) in diabetic compared with non-diabetic women. The UTI incidence rate was 72.8/1000 person-years (95% CI 70.6-75.0) in women with diabetes. The incidence was higher in women with previously diagnosed diabetes mellitus than in women who were recently (within 6 months) diagnosed (91.9/1000 person-years, 95% CI 84.3-99.4 vs. 70.5/1000 person-years, 95% CI 68.2-72.8) (2*).

Confounders such as age or increased regular check-ups resulting in more diagnostic investigations may be the basis for the increased infection rates found in patients with diabetes. A study analysing healthcare-associated infections in Turkey found that UTI was the most common infection in patients with diabetes mellitus (37.2% of all infections), which was significantly higher compared to patients without diabetes mellitus (29.8%). However, after adjusting for age and sex, no difference in UTI incidence between patients with and without diabetes mellitus was present (3*).

Risk factors for diabetes mellitus

Prevalence of ASB and incidence of UTI differ within women with diabetes mellitus. These differences can possibly be attributed to additional risk factors of the patient such as the existence of comorbidities or medication use.

Al-Rubeaan *et al*. (4**) studied 1,000 Saudi diabetic patients to assess prevalence and risk factors for UTI. Risk factors found to be associated with UTI were female sex (relative risk (RR) 6.10, 95% CI 4.34-8.57), hypertension (RR 1.20, 95% CI 1.06–1.36), insulin therapy (RR 1.41, 95% CI 1.26–1.58), BMI greater than 30kg/m^2 (RR 1.72, 95% CI 1.53-1.94) and nephropathy (microalbuminuria) (RR 1.42, 95% CI 1.04–1.94).

In addition, a study (n=3,152) using pooled safety data of 12 trials reported that treatment of type 2 diabetes with a recently developed sodium-glucose cotransporter-2 (SGLT2) inhibitor, dapagliflozin, was accompanied by a very small increased risk (SGLT2, 2.5mg 3.6%, 5mg 5.7% or 10mg 4.3% vs. placebo, 3.7%) of UTI compared to placebo. SGLT2-inhibitors are a new class of oral diabetes medication. These agents induce renal glucosuria by selectively targeting the renal SGLT2 transporter in patients with type 2 diabetes mellitus (5**). A smaller (n= 551) randomised control trial comparing the SGLT2 canagliflozin with placebo or sitagliptin found a slightly increased risk of ASB and UTI 12 weeks after start with the medication, but this did not reach statistical significance (ASB, 7.7% vs 6.3%, odds ratio (OR) 1.23, 95% CI 0.45-3.98; UTI, 5.0% vs 3.8% OR 1.31, 95% CI 0.45-4.68) (6**).

Complications

Serious and well known consequences in patients with diabetes mellitus involve pyelonephritis, including emphysematous pyelonephritis, bacteraemia and urosepsis. Tsu *et al.* (7*) confirmed in a retrospective study that most (66.7%) patients with emphysematous pyelonephritis suffered from diabetes. High tissue glucose levels, creating a favourable environment for the growth and multiplication of microorganisms, might be one of the aspects in the pathogenesis of this severe kind of pyelonephritis. A case report described bilateral emphysematous pyelonephritis caused by *Escherichia coli* in combination with a splenic abscess in a 66-year-old woman with untreated diabetes (8).

A number of recently published studies focused on the association between UTI and bladder or kidney function. Chiu *et al*. showed that UTI in diabetic patients with late-stage chronic kidney disease was associated with reversible superimposed acute kidney injury (9**). In addition, recurrent UTI was found to be associated with impaired voiding function and diabetic bladder dysfunction in women with type 2 diabetes mellitus (10*). Diabetes mellitus with complications was an independent predictor of major abnormalities (for instance hydronephrosis or urolithiasis) on ultrasonography or computed tomography scan in adult patients with community-acquired urosepsis (11). In addition, a study of 271 *E. coli* random urine and bloodstream isolates in Taiwan by Wang *et al.* (12*) demonstrated that poorer glycaemic control and more virulent *E. coli* isolates were more often associated with the presence of urosepsis in diabetic patients (80% women) than the presence of only ASB or UTI in this patient group.

Treatment

Guidelines recommend not to treat ASB in diabetic patients (13). Despite the fact that UTI in patients with diabetes mellitus is associated with more, severe and uncommon complications, trials addressing the optimal treatment of UTI are missing. Some studies report on difference in recurrence rates after treatment with different antibiotics, which may provide some guidance when treating UTI in patients with diabetes mellitus. Wang *et al.* (12*) reported similar antimicrobial resistance patterns of *E. coli* isolates between patients with and without diabetes. Only resistance for second- and third-generation cephalosporins was higher in patients with diabetes mellitus (24-25% vs. 12-14%).

Asymptomatic bacteriuria and urinary tract infection in pregnant women
Pregnant women are a vulnerable group when it comes to UTI's, not only because of the differences in pathophysiology or the limited treatment options but also because of the possible impact of the infection and treatment on both the mother and the neonate.

Epidemiology
Several studies were published on prevalence of ASB in pregnancy. In general the studies were of poor quality: small sample size, prevalence of ASB diagnosed at different gestational ages or the definition of ASB not clearly defined.

In a prospective cohort study performed in India, 371 pregnant women were screened for ASB before 20 weeks' and 274 women between 32 and 34 weeks' gestation. The prevalence of ASB was 17% in early pregnancy and 16% in the third trimester. Even though all pregnant women with ASB received antimicrobial treatment, an increased incidence of preterm labour (RR 3.27, 95% CI 1.38-7.72) and neonatal weight below the 10th percentile (RR 3.79, 95% CI 1.80-7.97) was found in women with ASB in the third trimester compared to women without ASB. No differences were found between women with and women without ASB in early pregnancy (14**).

Another study performed in Nigeria showed a 40% prevalence of ASB (50 of 124 women) in pregnant women between 9 and 24 weeks' gestation. Surprisingly, *Staphylococcus aureus* (72%) and *Proteus spp* (14%) and not *E. coli* (4%) were the most common pathogens (15). In other studies, *S. aureus* is only found in around 5% of the cases (16). These findings suggest that contamination with skin flora instead of real bacteriuria was present in the majority of patients. Unfortunately the authors do not provide a definition of 'significant' growth or 'positive culture' in the methods (15).

Studies focusing on the occurrence of UTI during pregnancy published recently used population-based data. Bruce *et al.* (17*) analysed data of 37,741 pregnancies of patients registered at a health maintenance organisation in Georgia and found UTI to be one of the five most common conditions during pregnancy (12%). The incidence of UTI during pregnancy studied in 4,501 Jordan women was even higher (20.2%) (18) In the Netherlands, UTI is the most frequent reason for a GP visit during pregnancy. UTI diagnosis was more common in pregnant compared to non-pregnant women (14 vs. 6 per 100 pregnant women) (19).

Concluding, both ASB and UTI are common during pregnancy; however, the found prevalence and incidence rates were widespread, possibly due to a combination of differences in diagnostic techniques, timing of urine collection and/or in cut-off points for significant bacteriuria.

Risk factors
During pregnancy, physiologic and physical changes such as decreased peristalsis of the urinary tract facilitate the growth of bacteria which may result in ASB or UTI (20).

A secondary analysis of an observational study with 4,490 pregnant women showed that a BMI of 35kg/m^2 or higher was associated with an increased risk for UTI in pregnancy (10.2-18.3% vs. 6.2-7.6%) (21*). Another interesting finding was that pregnant women

living with a cat or dog not only had an increased *E. coli* colonization of the vaginal flora, but also a higher incidence of self-reported UTI (with cat 32%, dog 27%, without a cat or dog 21%) indicating possible transmission of uropathogens between pets and pregnant women (22**).

Uropathogens
E. coli predominantly causes ASB and UTI; however other causative uropathogens such as Group B *Streptococcus* (GBS) are more often identified in pregnant women (16).

Currently GBS bacteriuria in pregnancy receives more attention because GBS bacteriuria indicates more heavy colonization than vaginal GBS colonization. This theory is endorsed by the findings of Kessous *et al*. (23*) who demonstrated that GBS bacteriuria is associated with higher rates of obstetric complications including intrapartum fever and chorioamnionitis compared with women with vaginal GBS colonization or no colonization. Finally, the authors found that pregnant women with GBS bacteriuria more often suffered from diabetes mellitus (23*). Unfortunately, the implications for clinical practice are not clear. A recent Cochrane review (24*) on intrapartum antibiotics for known maternal GBS colonization concluded that there is still not enough valid information from the existing three small, dated and biased trials to inform clinical practice. However a recent guideline developed by the Society of Obstetricians and Gynaecologists of Canada based on papers published before 2011 recommended providing intra-partum antibiotics when a woman is known to have GBS bacteriuria of any colony count, to prevent early-onset neonatal GBS disease (25).

Complications
It is important to realize that UTIs during pregnancy may affect not only the mother but also the neonate. Jolley *et al*. (26**) described hospitalization rates for pyelonephritis during pregnancy using US data from the Nationwide Inpatient Sample 2006. Cases of pyelonephritis were selected using ICD-9 codes, identifying 28,923 women with pyelonephritis (0.6% of all pregnant women). Concomitant diagnoses in women with pyelonephritis were septicaemia (1.95%), acute respiratory failure (0.77%), preterm labour or premature rupture of membranes (PROM) (3.77%), anaemia (22.4%) or diabetes mellitus (3.7%). Some pregnant women with pyelonephritis died during their hospital admission, underscoring the danger of this condition; however, no actual number was provided (26**).

A retrospective study from Jamaica found an incidence of 0.7% (102 in 14,651 deliveries) of confirmed pyelonephritis cases in pregnant women. Most cases (58.8%) were diagnosed in the second trimester. In only 59 of the 102 cases was a positive urine culture present; in other cases, the urine culture was negative, contaminated or missing (27*). In a retrospective cohort study, no differences were found in maternal morbidity (defined as days of admission) between pyelonephritis diagnosis antepartum and up to six weeks postpartum (28*).

Recent studies have focussed particularly on consequences of maternal UTI on the neonate. Collier *et al.* (29*) found that a combination of ASB, UTI and pyelonephritis during pregnancy in mothers with and without asthma was related to increased asthma

in offspring until six years of age (adjusted OR 1.60, 95% CI 1.12-2.29). This has already been described in other studies. For this recent study, 1,428 pregnant women with and without asthma were interviewed and maternal medical records were checked. No other maternal infections were associated with childhood asthma (29*). .

A case-control study comparing the association between antenatal maternal UTI and neonatal UTI showed that neonates admitted for the management of a UTI more often had a mother with a history of UTI compared to neonates admitted for jaundice (30.0% vs. 6.8% OR 5.9, 95% CI 1.9-18.3). A possible explanation for this association is sharing of genetic make-up and/or uropathogens in one household. A limitation of this study is the risk of recall bias as the mothers retrospectively reported the occurrence of maternal UTI and the authors did not give a clear definition of UTI (30*).

A review published last year by Cunnington *et al*. (31*) identified five studies describing the association between UTI and preterm delivery. Only one study showed that the risk of preterm birth was nearly doubled in pregnant women with compared to those without a UTI (RR 1.35, 95% CI 1.32-1.38). Three other studies showed a modest increase with point estimates between 1.03 and 1.09 and one study did not show any difference (RR 0.99, 95% CI 0.91-1.08) (31*) Incidence of UTI recorded in 911 medical files of French Caribbean women during pregnancy was increased in women who delivered preterm (<37 weeks) compared with women who delivered term (hazard ratio 1.9, 95% CI 1.3-2.8) (32).

A large, retrospective, population-based study analysing 219,612 singleton pregnancies found an incidence of acute antepartum pyelonephritis of 0.07% and demonstrated that antepartum pyelonephritis was an independent risk factor for preterm delivery (OR 2.6, 95% CI 1.7-3.9) (33*).

Treatment of asymptomatic bacteriuria and urinary tract infection in pregnancy
Guidelines still advice screening and treating ASB in pregnancy, although the evidence might be outdated. As far as we know, no studies concerning optimal treatment of ASB in pregnancy were published recently. Concerning the treatment of ASB or UTI, it has to be noted that treatment of UTI during pregnancy can be difficult, as certain antibiotics cannot be used. Currently, a cohort study with an embedded randomised controlled trial is being performed to address this issue in a modern population in the Netherlands, where screening and treating of ASB is not part of standard clinical practice (34).

Pregnant women often experience recurrent UTI. A Cochrane review on preventing recurrent UTI in pregnant women, with as primary outcomes recurrent UTI before birth (variously defined) and preterm birth (before 37 weeks), included only one small trial comparing a daily dose of nitrofurantoin and close surveillance with close surveillance alone. No differences were found between the two interventions on the primary outcomes and only a significant reduction in ASB was seen in women who received close surveillance and nitrofurantoin. This review highlighted that more trials are necessary to assess the optimal intervention to prevent recurrent UTI in pregnant women (35*).

The authors of another Cochrane review addressed the effectiveness of cranberries to prevent UTIs in pregnant women and concluded that cranberries are not effective (RR 1.04, 95% CI 0.93-1.17). This was based on the results of two studies, both reporting a high number of withdrawals possibly because of the large quantities of consumed cranberry juice, which can result into nausea especially during pregnancy (36*).

Addressing the choice of the right antimicrobial agent was done in a Spanish retrospective observational study. The investigators analysed 50 isolated microorganisms of 93 pregnant women with pyelonephritis and found that 10% of the cases were not properly treated with an antibiotic that matched the causative pathogen and its resistance pattern. In 46.2% of women with a diagnosis of pyelonephritis, no microorganisms were found, possibly as empirical treatment was commenced before a urine culture was performed (37*).

Consequences of antibiotic treatment during pregnancy
After the publication (2008) of the 7-year follow-up of the ORCALE II trial , which showed an increased risk of cerebral palsy in neonates whose mother received antibiotics during pregnancy, more studies focussed on possible adverse effects of maternal antibiotic use during pregnancy (38).

Wright *et al.* (39**) found that early-onset sepsis caused by antibiotic-resistant microorganisms in neonates was associated with maternal antibiotic use during pregnancy and delivery, including antibiotics for bacteriuria (6% of prescriptions). Main indications for antibiotic prescriptions were PPROM and chorioamnionitis (39**).

Short-term follow-up data of maternal nitrofurantoin use in a population based cohort showed no increased risk of major malformations (OR 0.79, 95% CI 0.55-1.23) , and only a small increased risk of neonatal jaundice when dispensed in the last 30 days before delivery (OR 1.31, 95% CI 1.02-1.70) (40**). However, in a long-term Danish follow-up study, 447,629 singleton pregnancies were followed to 9.9 years to investigate the relationship between maternal antibiotics use (mainly for UTI) and epilepsy. The investigators found a slightly increased risk of epilepsy in children whose mothers received antibiotic prescriptions (i.e. nitrofurantoin) during pregnancy; this was most pronounced among mothers with multiple prescriptions (hazard ratio 1.3, 95% CI 1.0-1.8). More research is needed to investigate confounding and the direct drug effect (41**).

CONCLUSION

The recently published papers concerning epidemiology and risk factors of ASB and UTI in diabetic and pregnant women mainly confirmed existing knowledge. Adverse effects of treatment of diabetes mellitus and bacteriuria itself were emerging topics. The newly developed type 2 diabetes mellitus agents, SGLT2-inhibitors, were found to be associated with a small increased risk for UTI due to increased glucosuria. In addition, antibiotic treatment of ASB or UTI during pregnancy was related with short-term and long-term consequences in the neonate. In the light of the possible adverse effects of antibiotics, more studies exploring the possibilities for non-antibiotic interventions to prevent or treat ASB and UTI are needed. Moreover, evidence regarding optimal treatment of UTI in diabetic patients is still lacking. Also, up-to-date studies investigating whether screening and treatment of ASB is still useful (including GBS bacteriuria during pregnancy) are necessary to inform clinical practice.

KEY POINTS

1. Due to the increased urine glucose excretion, the newly developed sodium-glucose cotransporter-2 inhibitors for the treatment of diabetes mellitus type 2 are associated with a very small increased risk of urinary tract infections (UTIs).

2. Diabetes mellitus with complications is an independent predictor of major abnormalities (for instance hydronephrosis or urolithiasis) on imaging in adult patients with community-acquired urosepsis.

3. Group B *Streptococcus* (GBS) bacteriuria is more common in pregnant women and associated with adverse pregnancy complications such as chorioamnionitis, but treatment implications for clinical practice are not clear.

4. Recently more attention has been drawn to the effects of antibiotic treatment of ASB or UTI during pregnancy, which may have long-term consequences for the neonate such as epilepsy and antibiotic resistance. More research is needed to further explore and confirm these findings.

5. The outdated evidence of the effects of ASB in combination with the possible negative effects of antibiotics used to treat ASB during pregnancy warrants up-to-date research about the ASB screening and treatment policies during pregnancy.

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