

# Asymptomatic Bacteriuria and Urinary Tract Infection in Pregnant Women with and without Diabetes Mellitus and Gestational Diabetes Mellitus—A Case-Control Study

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## Abstract

**Background:** Asymptomatic bacteriuria (ASB) and urinary tract infections (UTI) during pregnancy may contribute to adverse pregnancy outcomes. Diabetes mellitus (DM) and gestational diabetes mellitus (GDM) are considered to be important additional risk factor for ASB and UTI during pregnancy.

**Aims:** To investigate differences in prevalence of ASB and incidence of UTI in pregnant women with and without DM and GDM to inform ASB screening and treatment policies. **Methods:** Data from 214 pregnant women who gave birth during 2010 at the Women's and Children's Hospital, Adelaide, Australia where cases were women with a clinical diagnosis of (G)DM and controls were matched on date of birth. ASB was defined as the growth of at least 10e5 colony forming units/ml of one organism or any presence of group B streptococcus (GBS) at the first urine culture collected during pregnancy without complaints of a UTI. A clinical UTI was diagnosed by the treating physician, in combination with a positive urine culture it was defined as culture-confirmed UTI. **Results:** No significant differences in prevalence of ASB (5.6% and 3.7%; relative risk (RR) 1.50; 95% confidence intervals (CI) 0.44 - 5.17), incidence of clinical UTI (4.7% and 11.2%; RR 0.42; 95% CI 0.15 - 1.14) or culture-confirmed UTI (2.8% and 3.7%; RR 0.75; 95% CI 0.17 - 3.27) between pregnant women with and without (G)DM were present. No association was found between ASB and UTI. GBS was the most common causative

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organism of ASB in women with and without DM (66.7% and 50.0%). **Conclusion:** In contrast with earlier research, no significant differences in prevalence of ASB or incidence of UTI was found between pregnant women with and without (G)DM.

### Keywords

Urinary Tract Infections, Bacteriuria, Diabetes Mellitus, Pregnancy, Antenatal Screening

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## 1. Introduction

In the 1960s, Kass and colleagues described the association of untreated asymptomatic bacteriuria (ASB), bacteriuria without symptoms of a urinary tract infection (UTI), with preterm birth and perinatal mortality [1] [2]. However, subsequent studies showed contradictory results. The prevalence of ASB in pregnancy is 2% - 10%, although prevalence rates up to 40% have been reported [3] [4]. Earlier studies demonstrated that 30% to 40% of pregnant women with untreated ASB developed pyelonephritis [1] [4] [5]. The hypothesis is that anatomical and physiological changes occurring during pregnancy facilitate bacterial growth and ascent of the bacteria to the kidneys [6]. This led to further research and the introduction of ASB screening and treating policies in many countries.

A systematic Cochrane review on the effect of antibiotic treatment for asymptomatic bacteriuria in pregnancy concluded that treatment of ASB reduces pyelonephritis, low birth weight and preterm birth [4]. However the reduction in low birth weight and preterm birth found in this review has to be interpreted with care, given the poor quality of studies [4].

A more recent study in over 5000 pregnant women in the Netherlands, where currently no standard screen-and-treat policy for ASB during pregnancy is in place, found that ASB was not related to preterm birth in women with an uncomplicated singleton pregnancy. Furthermore, they found that the absolute risk of pyelonephritis in pregnant women with untreated ASB is low (2.4%) [7].

Recent studies have revealed possible adverse effects of maternal antibiotic use during pregnancy including malformations, cerebral palsy and the presence of antibiotic resistant microorganisms in the newborn [8] [9].

In most countries, including Australia, screening and treatment of ASB during pregnancy to prevent adverse pregnancy outcomes is recommended [10]. This is even though the association between ASB and perinatal morbidity have not been clearly established and the whole range of possible side effects of maternal antibiotic use during pregnancy is not wholly identified yet and currently further investigated [4] [9] [10] [11] [12] [13].

Diabetes mellitus (DM) and gestational diabetes (GDM) are considered important additional risk factor for both ASB and UTI in pregnant women [14] [15]. Furthermore the incidence of GDM is increasing in high-income countries such as Australia [16]. Previous studies with mainly small sample sizes have re-

ported similar or increased prevalence of ASB up to 24% in pregnant women with DM compared to women without DM [17] [18] [19].

The incidence of symptomatic UTI is higher in pregnant women with DM (3.3% - 8.8%) compared to women without DM (1.3% - 2.3%) [12] [17] [19] [20]. Pregnant women with ASB more often develop a symptomatic UTI when they have DM compared to those without DM [17].

Many guidelines have been adopted in favor of a screen and treat strategy to prevent complications in pregnant women with ASB [10] [21]. It remains important to challenge this approach because the truly achieved reduction of complications in pregnancy following the screen and treat approach has to be balanced against the side effects of antibiotics for both mother and baby and the unnecessary costs [8] [9] [22] [23].

This study aimed to describe current practice in a developed country, Australia, and to provide more background for ASB screening and treatment policies, especially for high-risk pregnant women with GDM or DM. The specific aims were to investigate differences in prevalence of ASB and incidence of UTI, including causative organisms, in pregnant women with and without DM or GDM.

## 2. Methods

### 2.1. Design and Patients

For this case-control study we used data from pregnant women with DM or GDM (cases) and without DM or GDM (controls) who received antenatal care in the Women's and Children's Hospital in Adelaide, Australia, during 2010. In Australian guidelines routine urine examination during antenatal assessment is advised and was part of standard care in the Women's and Children's Hospital in Adelaide [24] [25].

Cases were randomly selected using systematic sampling with an interval length of two (alternating) on the basis of a list with names of all women who gave birth during 2010 and who were diagnosed with DM or GDM (according to the hospital administration). Controls were randomly collected from a list of women in the same period. To make the two samples comparable, controls with the same birth dates as the cases were selected. Obstetric, demographic and laboratory data were extracted from medical records up to six weeks postpartum. Women were ineligible if they had no available urine culture result, no access to the medical record, a multiple pregnancy, anatomical abnormalities of the urinary tract or pre-existing medical conditions with a known association with UTI except for pregnancy and diabetes. The Hospital Research and Ethics Committee provided ethical approval.

### 2.2. Definitions

ASB was defined as the growth of at least  $10^5$  colony forming units (cfu)/ml of one organism or any presence of group B streptococcus (GBS) at the first urine culture (screening urine sample) collected during pregnancy without complaints

of a UTI. A clinical UTI was defined as a clinical diagnosis made by the treating physician (UTI registered by the treating physician in the clinical record); a culture confirmed UTI was defined as a clinical UTI in combination with a positive urine culture. When women were admitted because of a UTI it was considered to be for pyelonephritis. Recurrent UTI (RUTI) was defined following treating physician. Urine cultures with growth less than  $10^5$  cfu/ml or with growth of more than two organisms were defined as mixed growth. Urine cultures without growth were defined as negative. Both DM (type 1 and type 2) and GDM were clinical diagnoses. Screening for GDM with a 50 gram oral glucose challenge test between 24 to 28 weeks gestation was part of standard care in the Women's and Children's Hospital in Adelaide during the study period. Small for gestational age (SGA) was defined as birth weight in relation to gestational age smaller than the 10th percentile, appropriate for gestational age (AGA) between the 10th and 90th percentiles and large for gestational age (LGA) greater than 90th percentile [26].

### 2.3. Outcomes

The primary outcome was the prevalence of ASB diagnosed from the first available antenatal urine culture, as most guidelines recommend collecting urine during the first antenatal visit. Other outcomes were the incidence of both clinical and culture confirmed UTI including pyelonephritis, postpartum UTI (up to 6 weeks after birth), and causative uropathogens. Furthermore, the association between ASB and development of UTI was investigated.

The following maternal and neonatal characteristics were assessed: maternal age at birth, parity, race, type of DM (type 1, 2 or DMG), treatment of DM (insulin, oral hypoglycaemics and/or diet), history of recurrent urinary tract infections (RUTI), use of prophylaxis or antibiotics two weeks before first urine culture, mode of birth (normal vaginal birth, operative vaginal birth, caesarean section), gestational age at birth (categorized as <32, 32 - 37, 37 - 40 and >40 weeks' gestation), gender child, SGA, LGA, AGA, admission to neonatal intensive care unit independent of duration, five minute Apgar score less than seven, neonatal antibiotic use and positive neonatal blood cultures.

### 2.4. Statistics

Data were analyzed using SPSS software for windows, version 19. Fisher's exact test and the Mann-Whitney test were used to calculate differences in characteristics of the women and infants born from women with and without DM. Relative risk (RR) and 95% confidence intervals (95% CI) was calculated to estimate differences in binary outcomes. The Mann-Whitney test was used test differences for continuous outcomes.

## 3. Results

### 3.1. Maternal and Neonatal Characteristics

A total of 214 pregnant with DM and GDM ( $n = 107$ ) and without DM and

GDM (n = 107) were eligible for analysis (Figure 1). The 107 women with DM and GDM represent around 30% of the total number of pregnant women with DM who gave birth at the Women's and Children's Hospital during the year. Demographics of both groups were similar (Table 1(a) and Table 1(b)). Of the

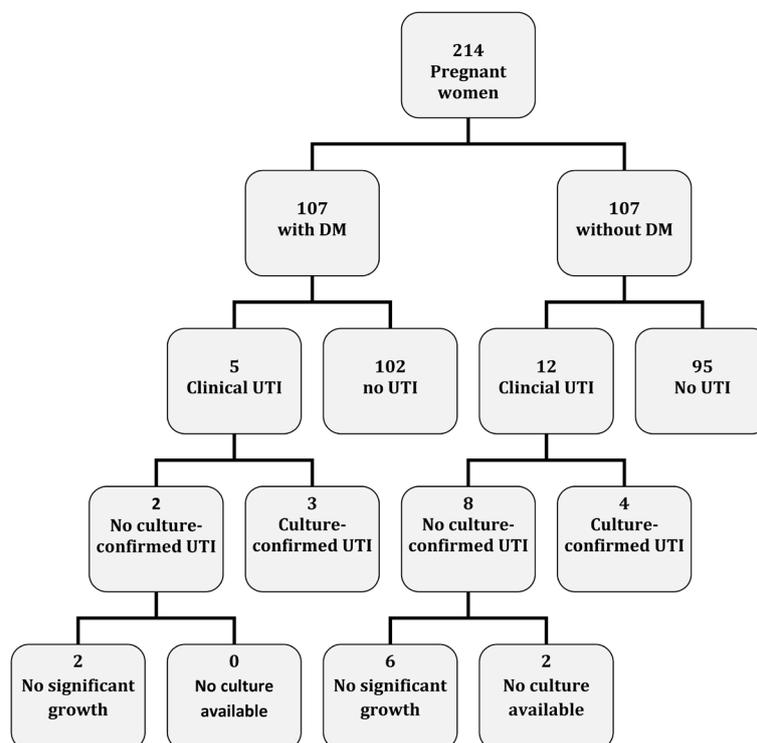
**Table 1.** (a) Maternal characteristics for women with and without DM or GDM; (b) Neonatal characteristics for infants born to women with or without DM.

(a)					
	With DM (n = 107)		Without DM (n = 107)		P-value <sup>a</sup>
Age (years)	31.3 ± 5.4		29.6 ± 5.0		0.021
Ethnicity					
▪ Caucasian	55	51.4%	55	51.4%	0.963
▪ Asian	43	40.2%	41	38.3%	
▪ Aboriginal	3	2.8%	3	2.8%	
▪ Other or mixed	6	5.6%	8	7.5%	
History of RUTI	1	0.9%	4	3.7%	0.369
Multipara	29	27.1%	22	20.6%	0.336
Type of DM					
▪ Type 1	3	2.8%	-	-	-
▪ Type 2	6	5.6%	-	-	
▪ GDM	98	91.6%	-	-	
Treatment diabetes					
Insulin	18	16.8%	-	-	-
Oral hypoglycemics	40	37.4%	-	-	-
Diet	105	98.1%	-	-	-

Note: Figures are numbers and percentages; or mean and standard deviation; <sup>a</sup>p-value calculated either with Fisher's exact test or Mann-Whitney test. Abbreviations: DM = diabetes mellitus; GDM= gestational diabetes mellitus; RUTI = recurrent urinary tract infection.

(b)					
	With DM (n = 107)		Without DM (n = 107)		P-value <sup>a</sup>
Gender					
▪ Male	56	52.3%	59	55.1%	0.784
▪ Female	51	47.7%	48	44.9%	
Weight & gestational age					
▪ SGA	9	8.4%	8	7.5%	0.631
▪ AGA	77	72.0%	83	77.6%	
▪ LGA	21	19.6%	16	15.0%	
Pregnancy duration					
▪ <32 weeks	0	-	2	1.9%	0.004
▪ 32 - 37 weeks	6	5.6%	3	2.8%	
▪ 37 - 40 weeks	82	76.6%	63	58.9%	
▪ >40 weeks	19	17.8%	39	36.4%	
Apgar at 5 minutes <7	2	1.9%	5	4.7%	0.445
Admission to NICU	4	3.7%	1	0.9%	0.369
Antibiotic use < 6 weeks	18	16.8%	18	16.8%	1.000
Positive blood culture <6 weeks	0	-	1	0.9%	1.000

Abbreviations: DM = diabetes mellitus; SGA = small for gestational age; AGA= appropriate for gestational age; LGA= large for gestational age; NICU = neonatal intensive care unit. <sup>a</sup>p-values calculated using the Fisher's exact test.



**Figure 1.** Flow-diagram urinary tract infections in pregnant women with and without DM and GDM. Abbreviations: DM = diabetes mellitus; AB = antibiotics; GA = gestational age; ASB = asymptomatic bacteriuria; UTI = urinary tract infection; GBS = Group B streptococcus. Definitions: ASB was defined as the growth of at least  $10^5$  cfu/ml of one or two organisms or any presence of group B streptococcus at the first urine culture collected during pregnancy without complaints of a UTI; Clinical UTI was defined as clinical diagnosis made by the treating physician; Culture confirmed UTI was defined as clinical UTI in combination with a positive urine culture; Positive culture was defined as growth of at least  $10^5$  cfu/ml of one or two organisms.

107 women, most were diagnosed with GDM ( $n = 98$ , 91.6%), of whom 59 (60.2%) were treated with diet alone, 33 (33.7%) received oral hypoglycaemics and 10 (10.2%) used insulin. Part of the women received more than one type of diabetes treatment during their pregnancy. Women without diabetes or GDM more frequently gave birth after 40 weeks of gestation.

### 3.2. ASB and UTI

The mean gestational age at the time of first urine sample was between 11 - 12 weeks gestation for both diabetic and non-diabetic women (11.4, Standard deviation (SD)  $\pm 4.2$  and 11.3, SD  $\pm 4.5$  weeks). The overall prevalence of ASB was 4.7% and no differences were found between women with and women without DM (5.6% and 3.7%; relative risk (RR) 1.50; 95% confidence intervals (CI) 0.44 - 5.17) (Table 2). Group B Streptococcus (GBS) was the most common causative organism of ASB (60%) followed by *Escherichia coli* (*E. coli*) (30%). No association was found between ASB and UTI during pregnancy.

One woman with DM (0.9%) and four (3.7%) women without DM had symptoms of a UTI at the time of the first urine culture 'the screening urine' and were

**Table 2.** Relative risks for urine results in women with and without DM.

	With DM (n = 107)		Without DM (n = 107)		RR (95% CI) or p-value <sup>a</sup>
Antenatal ASB					
GA at first urine result (weeks)	11.4 ± 4.2		11.3 ± 4.5		0.609
AB use < 2 weeks for “ASB screening”	2	1.9%	2	1.9%	-
Results first urine culture “ASB screening”					
▪ <i>ASB without GBS</i>	2	1.9%	2	1.9%	0.5260
▪ <i>GBS ASB</i>	4	3.7%	2	1.9%	
▪ <i>Culture-confirmed UTI</i>	1	0.9%	4	3.7%	
▪ <i>No significant growth</i>	100	93.5%	99	92.5%	
Total ASB including GBS first culture	6	5.6%	4	3.7%	1.50 (0.44 - 5.17)
Antenatal UTI					
Clinical UTI	5	4.7%	12	11.2%	0.42 (0.15 - 1.14)
Culture-confirmed UTI	3	2.8%	4	3.7%	0.75 (0.17 - 3.27)
Received AB treatment for clinical UTI	5	4.7%	11	10.3%	0.46 (0.16 - 1.26)
Admission for UTI (pyelonephritis)	1	0.9%	1	0.9%	1.00 (0.06 - 15.78)
ASB associated with development of clinical UTI (n = 10)	0	-	0	-	-
Post-partum					
Clinical UTI	3	2.8%	1	0.9%	3.00 (0.32 - 28.39)
Culture-confirmed UTI	1	0.9%	1	0.9%	1.00 (0.06 - 15.78)
Admission for UTI (pyelonephritis)	0	-	1	0.9%	-

Abbreviations: DM = diabetes mellitus; AB = antibiotics; GA = gestational age; ASB = asymptomatic bacteriuria; UTI = urinary tract infection; GBS = Group B streptococcus; RR = relative risk; 95% CI = 95% confidence intervals. Definitions: ASB was defined as the growth of at least 10e5 cfu/ml of one or two organisms or any presence of group B streptococcus at the first urine culture collected during pregnancy without complaints of a UTI; Clinical UTI was defined as clinical diagnosis made by the treating physician; Culture confirmed UTI was defined as clinical UTI in combination with a positive urine culture; Positive culture was defined as growth of at least 10e5 cfu/ml of one or two organisms. <sup>a</sup>RR and 95% CI for binary variables; p-values calculated with Mann-Whitney test for continuous variables.

therefore diagnosed as UTI or pyelonephritis. Only one pregnant woman with ASB received antibiotic treatment. All women with GBS bacteriuria at the first urine culture received antibiotic prophylaxis during birth.

No differences in clinical UTI during pregnancy were seen in pregnant women with and without DM (4.7% and 11.2%; RR 0.42; 95% CI 0.15 - 1.14). In seven of the 17 women with a clinical UTI, a positive culture was present (culture confirmed UTI), in eight women there was a mixed growth, and in two women no culture results were available (**Figure 1**). Sixteen of the 17 clinical UTIs were treated with antibiotics. Two women (one with and one without DM) were admitted because of a UTI during pregnancy.

No differences in incidence of culture confirmed UTI, including pyelonephritis, during pregnancy (2.8% and 3.7%; RR 0.75; 95% CI 0.17 - 3.27) and post-partum (0.9% and 0.9%; RR 1.00; 95% CI 0.06 - 15.78) were found between women with and without DM. In both pregnant women with and without DM, *E. coli* was the most common causative organism of UTI. *GBS* was not the causative organism for any of the UTIs.

In both women with and women without diabetes or GDM no association was found between ASB or clinical UTI during pregnancy and adverse pregnancy or neonatal outcomes, including preterm birth and SGA.

#### 4. Discussion

In our study, based on clinical practice ASB screening data, we found that the overall prevalence of ASB was rather low (4.7%). Moreover, no differences in prevalence of ASB or incidence of culture confirmed UTI and clinical UTI was present between pregnant women with and without DM or GDM. Group B streptococcus was the most common causative organism of ASB in both women with and without DM.

No association was seen between ASB or UTI and adverse pregnancy outcomes including preterm birth (<37 weeks) or SGA babies. Although it should be pointed out that the study groups were small and therefore this dataset was only able to detect large differences in pregnancy outcomes.

Little is known about the practical implementation and the efficiency of screening and treating policies for ASB to prevent adverse pregnancy outcomes in pregnant women generally and especially in pregnant women with DM or GDM. The strength of this study is that it gives insight to the practical implementation and the efficiency of the actual screening and treating policy for ASB, including low colony count GBS bacteriuria, in a developed country (Australia) for both women with and without DM.

According to national and international guideline recommendations, there seems to be an under-treatment of ASB in pregnant women in this dataset, in contrast with UTIs. In this study, only for one in ten pregnant women with ASB was antibiotic treatment recorded. A possible explanation for this low treatment rate could be the high percentage of GBS ASB. There are no formal recommendations for management of low colony count GBS bacteriuria during pregnancy; even though GBS bacteriuria may indicate heavy vaginal GBS colonization [18]. In this study we did not find an association between GBS ASB and UTI.

One of the limitations of the study was that only hospital-records and laboratory database were available, while general practitioners could also have diagnosed and treated UTIs contemporaneously, which may not have been recorded in the hospital files. This may partly explain the reduced incidence of UTI in pregnant women with DM and GDM found in this study compared with earlier studies [17]. In addition, all women with GBS bacteriuria at the time of first urine culture received antibiotic prophylaxis during birth. Therefore, it is not possible to make conclusions about the effect of GBS ASB in the postpartum period.

Three earlier studies found either similar or increased percentages of ASB (including GBS ASB) in both pregnant women with DM (4.6% - 24%) and pregnant women without DM (4.0% - 10.9%) [7] [17] [18] [19]. Only Golan *et al.* showed an association between ASB and UTI in their prospective cohort study with monthly follow-up including repeating cultures. Among the pregnant women

with DM and ASB the incidence of UTI was 41.1% compared to 4.2% in those without ASB [17].

Nevertheless, in general accurate up-to-date numbers of ASB and UTI in pregnant women including causing organisms are not available due to a variety of reasons. Practice treatment is often started immediately when typical dysuria complaints are present without performing or awaiting for urine culture results. It may be difficult to distinguish between “real” UTI and pregnancy related symptoms, especially in pregnant women. Pregnancy symptoms, such as frequency and abdominal pain, impede the differentiation between ASB and UTI [2]. In order to make a contribution to accurate numbers we separated culture confirmed UTI and clinical UTI. It must be noted that detailed information on symptoms of UTI was often missing in the medical records.

This study reveals that for more than 50% of the time when antibiotics for UTI were prescribed during pregnancy there was no documented information about a positive urine culture available within the health records. The Australian guidelines state that a urine culture is the golden standard for all suspected UTIs [24] [25]. Performing a culture before commencing treatment should prevent over-treatment by discriminating between “real” UTI and pregnancy symptoms. Recent studies have shown that maternal antibiotic use during pregnancy can be associated with adverse effects for the newborn [8] [9].

## 5. Conclusion

Our study demonstrated that pregnant women with DM or GDM do not have an increased risk for ASB or UTI and that the overall prevalence of ASB in pregnant with and without DM or GDM was low and finally that GBS bacteriuria is common in both pregnant women with and without DM or GDM. Despite the limitations of the retrospective study design, these results are useful input for future discussions regarding ASB screening and treating policies for pregnant women currently in place in developed countries.

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