Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 192–195

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Asymptomatic pyuria in pregnant women during the first trimester is associated with an increased risk of adverse obstetrical outcomes

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ARTICLE INFO

Article history:
Accepted 15 April 2016

Keywords:
asymptomatic bacteriuria
low birth weight
preterm delivery
pyuria
urinalysis

ABSTRACT

Objective: Urinalysis is included in the prenatal examination in the first trimester in Taiwan, in contrast to Western countries. We aimed to investigate whether asymptomatic pyuria as detected by urinalysis was associated with adverse perinatal outcomes.

Materials and Methods: A total of 1187 singleton pregnant women who received prenatal care at Kaohsiung Chang Gung Memorial Hospital between January 2012 and December 2013 were included for retrospective analysis. We defined asymptomatic pyuria as the presence of 15 or more white blood cells/μL in midstream urine without symptoms. Adverse perinatal outcomes including preterm delivery, preterm premature rupture of membrane, low birth weight, and Apgar scores were analyzed. Univariate and multivariate logistic regression analyses were used to identify independent predictors.

Results: The prevalence of asymptomatic pyuria was 21.3% in our cohort. Univariate analysis showed that pyuria was the only factor associated with preterm delivery before 36 weeks of pregnancy, preterm premature rupture of membrane, and low birth weight. In multivariate analysis, both pyuria (odds ratio: 4.89, 95% confidence interval: 1.80–13.25, $p = 0.002$) and a maternal age of 35 years or older (odds ratio: 3.46, 95% confidence interval: 1.11–10.78, $p = 0.033$) were significant independent predictors for a low 5 minute Apgar score (<7).

Conclusion: The identification of asymptomatic pyuria via urinalysis in the first trimester may be a predictor for adverse perinatal outcomes.

Introduction

Urinary tract infections (UTIs) are the most common type of infection during pregnancy [1]. Pregnant women are at increased risk of UTIs because of anatomical and hormonal changes, which lead to ureteral dilatation and urinary stasis [2,3]. Asymptomatic bacteriuria (ASB) is the occurrence of a significant amount of bacteria in the urine without symptoms of infection. The diagnosis of ASB is based on laboratory cultures, and is marked by significant bacteriuria (defined as $\geq 10^5$ colony forming units/mL in urine cultures of a midstream specimen) with no clinical manifestations of infection [4,5]. The reported incidence of ASB ranges from 4% to 40% of pregnant women [6–10]. A previous study reported a strong association between untreated ASB during pregnancy and preterm delivery as well as low birth weight (LBW) [11]. As a result, performing routine *antepartum* urine cultures in the first trimester to screen for ASB is a standard practice in obstetric care, and is suggested by most antenatal guidelines worldwide [12–15].

However, urinalysis is the first step when evaluating a UTI. The benefits of urinalysis over cultures include a shorter examination time and a much lower cost. Pyuria is a laboratory finding defined as the presence of 15 or more white blood cells (WBC)/μL in the urine; however, contamination of urine samples may occur if squamous epithelial cells are present [16,17]. Women with symptomatic pyuria may have a UTI, and the gold standard for the diagnosis of a UTI is the presence of pathogens in a urine culture. The National Health Insurance program in Taiwan provides comprehensive prenatal care for all women, and urinalysis is included in the routine prenatal examination during the first trimester. However, no previous study has investigated the association between asymptomatic pyuria and poor pregnancy outcomes. In clinical practice, clinicians in Taiwan usually ignore

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http://dx.doi.org/10.1016/j.tjog.2016.04.040

asymptomatic pyuria and do not perform urine cultures or treat the condition because these pregnant women usually have their next visit in 1 month. Therefore, the purpose of this study was to evaluate whether untreated asymptomatic pyuria is associated with adverse perinatal outcomes.

Materials and methods

We conducted this 2-year retrospective study between January 2012 and December 2013. During this period, a total of 3249 pregnant women delivered their babies at Kaohsiung Chang Gung Memorial Hospital, Taiwan. Ethical approval was obtained from the Institutional Ethics Committee of Chang Gung Memorial Hospital (approval date May 26, 2015). The Institutional Review Board of Chang Gung Memorial Hospital approved the chart evaluation of this retrospective study. The inclusion criteria were as follows: (1) singleton pregnancy; (2) urinalysis data at the first trimester prenatal visit; and (3) babies that were delivered at our hospital. Quantitative urine WBC counts were measured using a hemocytometer (CLINITEK Atlas Automated Urine Chemistry Analyzer, Siemens, Munich, Germany). Pyuria was defined as the presence of 15 or more WBC/μL (equivalent to >5 WBC per high power field) in clean-voided midstream urine. If there were more than 15 squamous epithelial cells/μL in the urine sample, the sample was considered to be contaminated [16,17]. The exclusion criteria were women: (1) who delivered their fetus after medical induction earlier than 36 weeks of gestation due to variable reasons; (2) who received a cesarean delivery earlier than 36 weeks of gestation due to medical indications such as severe preeclampsia or others; (3) with symptomatic pyuria who had received medical treatment; and (4) with asymptomatic pyuria but suggestive of sample contamination.

Medical records were reviewed for demographic information including maternal age, gravidity, parity, body mass index (BMI) at first prenatal examination, WBC count in maternal plasma at the first trimester prenatal examination, results of screening urinalysis, pregestational diabetes, gestational diabetes, and the results of group B streptococcus cultures. Data on perinatal outcomes were obtained from maternal and neonatal medical records, and included gestational age at delivery, gestational age at rupture of the membrane if preterm, fetal birth weight, and Apgar score at 1 and 5 minutes.

SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Qualitative variables were compared using the Chi-square test, and quantitative variables were compared using the Student *t* test. Univariate and multivariate logistic regression analyses were used to identify factors predicting adverse perinatal outcomes. A p value < 0.05 was considered to be statistically significant.

Results

Of the 3249 women who delivered their babies at our hospital, 1234 met the inclusion criteria. Forty-seven of these 1234 women were further excluded for the following reasons: 21 due to medical induction earlier than 36 weeks (11 for medical indications such as severe preeclampsia and fetal distress; 3 for trisomy 21; 1 for trisomy 18; 2 for hydrops fetalis with intrauterine demise; 1 for acrania; and 3 for fatal structural abnormalities); 8 due to treatment for symptomatic pyuria; and 18 due to contaminated urine samples. The remaining 1187 pregnant women were then entered into the analysis; 934 had normal screening urinalysis data and 253 had pyuria. Thus, the prevalence of asymptomatic pyuria was 21.3% in our cohort. The clinical characteristics of the women with and without pyuria detected in first trimester urinalysis are shown in Table 1. The mean gestational age at delivery was significantly lower in the pyuria group (38.29 ± 3.50 weeks vs. 38.92 ± 1.90 weeks, $p = 0.006$). There was also a statistically significant higher rate of pregestational diabetes in the pyuria group (2.4% vs. 0.86%, $p = 0.048$). However, there were no significant differences in other clinical characteristics including maternal age, parity, BMI, gestational diabetes, maternal plasma WBC count, mode of delivery, and group B streptococcus colonization between the groups.

Table 1
Clinical characteristics of women with and without pyuria in first trimester urinalysis.

Characteristic	No pyuria $N = 934$ (%)	Pyuria $N = 253$ (%)	p
Maternal age (y)	33.16 ± 4.17	33.20 ± 4.29	0.296
Parity			0.342
Nulliparous	430 (46)	108 (42.7)	
Multiparous	504 (54)	145 (57.3)	
Gestational age at delivery (wk)	38.92 ± 1.90	38.29 ± 3.50	0.006
Preterm delivery before 36 wk	31 (3.3)	18 (7.1)	0.007
BMI (kg/m^2)	21.96 ± 3.33	22.78 ± 3.62	0.143
WBC count at first prenatal exam	8851 ± 2200	9049 ± 2263	0.918
Leukocytosis (>10.3 × 10^9/L)	115 (12.3)	27 (10.7)	0.476
Pregestational diabetes	8 (0.86)	6 (2.40)	0.048
Gestational diabetes	49 (5.25)	14 (5.54)	0.856
Delivery			0.064
Vaginal	669 (71.6)	196 (77.5)	
Abdominal	265 (28.4)	57 (22.5)	
GBS colonization			0.877
Yes	180 (19.3)	50 (19.8)	
No	581 (62.2)	166 (65.6)	
Unknown	173 (18.5)	37 (14.6)	

Data are expressed as means ± standard deviation or n (%). $p < 0.05$ was considered to be statistically significant.
BMI = body mass index; GBS = group B streptococcus; WBC = white blood cells.

The perinatal outcomes of the women with and without pyuria are presented in Table 2. There was a statistically significantly higher rate of preterm delivery before 36 weeks in the pyuria group (7.1% vs. 3.3%, $p = 0.007$), and also statistically significantly higher rates of preterm premature rupture of membrane (PPROM) in the pyuria group before 28 weeks (2.4% vs. 0.1%, $p < 0.001$) or 34 weeks of gestation (3.6% vs. 0.9%, $p = 0.001$). The mean fetal birth weight was significantly lower in the pyuria group (2999 ± 657 g vs. 3153 ± 486 g, $p = 0.007$), and the rate of LBW, defined as <2500 g, was higher in the pyuria group (9.1% vs. 5.1%, $p = 0.033$). The

Table 2
Perinatal outcomes of the women with and without pyuria in first trimester urinalysis.

Outcome	No pyuria $N = 934$(%)	Pyuria $N = 253$(%)	p
Admission of tocolysis			0.064
Yes	40 (4.3)	18 (7.1)	
No	894 (95.7)	235 (92.9)	
Preterm premature rupture of membrane			
<28 wk			<0.001
Yes	1 (0.1)	6 (2.4)	
No	933 (99.9)	247 (97.6)	
<34 wk			0.001
Yes	8 (0.9)	9 (3.6)	
No	926 (99.1)	244 (96.4)	
Preterm delivery before 36 wk	31 (3.3)	18 (7.1)	0.007
Birth weight, mean (g)	3153 ± 486	2999 ± 657	0.007
Low birth weight (<2500 g)	48 (5.1%)	23 (9.1%)	0.033
Apgar score			
1 min	8.86 ± 0.81	8.55 ± 1.70	0.006
5 min	9.89 ± 0.75	9.61 ± 1.72	0.011
1 min <7	13 (1.4)	14 (5.5)	<0.001
5 min <7	7 (0.8)	9 (3.6)	0.001

$p < 0.05$ was considered to be statistically significant.

Table 3
Univariate analysis of clinical factors associated with adverse outcomes including preterm delivery before 36 weeks, preterm premature rupture of membranes, low birth weight, low Apgar score (5 min <7); the presence of any one was considered as being an adverse outcome.

	Preterm OR (95% CI)	*p*	PPROM [a] OR (95% CI)	*p*	LBW OR (95% CI)	*p*	Low Apgar score OR (95% CI)	*p*
Pyuria	2.231 (1.23–4.06)	0.009	4.269 (1.63–11.18)	0.003	1.758 (1.04–2.97)	0.035	4.885 (1.80–13.25)	0.002
Advanced maternal age [b]	1.68 (0.94–3.01)	0.08	1.28 (0.49–3.34)	0.613	1.22 (0.75–1.97)	0.428	3.458 (1.11–10.78)	0.033
Obesity	3.11 (0.37–25.95)	0.294	—	0.998	1.11 (0.14–8.56)	0.924	—	0.998
Pregestational diabetes mellitus	3.99 (0.87–18.35)	0.075	5.56 (0.69–45.10)	0.108	1.23 (0.16–9.55)	0.843	—	0.999
Leukocytosis	1.24 (0.55–2.81)	0.61	1.59 (0.45–5.60)	0.471	1.09 (0.53–2.25)	0.812	1.05 (0.24–4.68)	0.947

CI = confidence interval; OR = odds ratio.
[a] PPROM was defined as preterm premature rupture of membranes before 34 weeks in this analysis.
[b] Advanced maternal age was defined as above 35 years. $p < 0.05$ was considered to be statistically significant.

neonates in the pyuria group also had a lower Apgar score (<7) at both 1 minute and 5 minutes compared with the neonates of the women without pyuria ($p < 0.001$).

In order to identify clinical parameters that may be associated with adverse perinatal outcomes including preterm delivery, PPROM, LBW, or low Apgar score at 5 minutes (<7), we performed univariate and multivariate analyses using a logistic regression model. In univariate analysis, pyuria was the only significant factor predicting preterm delivery [odds ratio (OR): 2.23, 95% confidence interval (CI): 1.23–4.06, $p = 0.009$], PPROM (OR: 4.27, 95% CI: 1.63–11.18, $p = 0.003$), and LBW (OR: 1.76, 95% CI: 1.04–2.97, $p = 0.035$). Other factors including maternal obesity, pregestational diabetes, and maternal plasma WBC count were not significant factors for adverse perinatal outcomes. Pyuria (OR: 4.89, 95% CI: 1.80–13.25, $p = 0.002$) and a maternal age of 35 years or older (OR: 3.46, 95% CI: 1.11–10.78, $p = 0.033$) were significant factors both in univariate and multivariate analyses to predict a low 5-minute Apgar score (<7; Tables 3 and 4).

Discussion

Screening for bacteriuria in early pregnancy is strongly recommended in many countries [14–16]. In Taiwan, routine screening is performed via urinalysis instead of urine cultures according to the policy of the National Health Insurance program for prenatal care. Therefore, the prevalence of asymptomatic UTIs cannot be compared with previous studies due to different screening methods. In previous studies, UTIs seem to be associated with preterm birth. The mechanism for such an association has yet to be clearly established, although it has been postulated to be through the production of phospholipase A2 by microorganisms, which then initiates labor through the activation of prostaglandin [18]. In a meta-analysis by Romero et al [11], asymptomatic bacteriuria was strongly associated with preterm delivery and LBW, and antibiotic treatment was effective in reducing the rate of LBW infants. Despite the reported association between asymptomatic bacteriuria and preterm delivery, other studies have reported different findings. For example, the Cardiff Birth Survey, which prospectively studied 25,844 births, reported that after adjusting for demographic and social factors, asymptomatic bacteriuria was not associated with preterm delivery [19]. In the current study, asymptomatic pyuria detected during urinalysis screening in the first trimester was associated with preterm delivery, LBW, and lower Apgar scores. In addition, our results revealed a strong association between pyuria and PPROM before 28 weeks or 34 weeks of gestation. However, a direct relationship between UTI and PPROM has seldom been mentioned in previous studies. During pregnancy, alterations in hormone levels result in changes in pH values in the lower genital tract, which aids the growth of anaerobic bacteria and other pathogenic microorganisms within the vagina. Genital tract infection is a well-established risk factor for PPROM [20], and pregnant women with genital tract infections have been reported to have a significantly increased risk of UTI [21]. Taken together, these findings indicate that UTIs may be a consequence of genital tract infections, and this may explain our finding of an association between pyuria and PPROM.

UTIs are one of the top 10 concurrent illnesses that occur in patients with diabetes [22]. Neutrophil function impairment in diabetic patients and micturition abnormalities secondary to diabetic neuropathy are the main reasons for the increased susceptibility to UTI. Increased prevalence rates of UTIs and asymptomatic bacteriuria have been described in women with diabetes compared with those without diabetes [23,24]. We also found that the pregnant women with pregestational diabetes had a higher rate of asymptomatic pyuria in the first trimester. Although pregestational diabetes has been reported to be associated with preterm delivery [25,26], there was no significant relationship between pregestational diabetes and poor perinatal outcomes in our study. The reason for this discrepancy may be the limited case numbers for women with pregestational diabetes.

According to the World Health Organization and National Institutes of Health definitions, obesity is defined as BMI $\geq$ 30 kg/m^2. Sebire et al [27] reported that UTIs occurred significantly more common in obese pregnant women in comparison with women with a normal BMI. Another study also reported that the incidence of UTIs was significantly higher in morbidly obese (BMI $\geq$ 40 kg/m^2) patients [28]. In our study, only 24 (2%) pregnant women had a BMI of 30 kg/m^2 or more, 7 of whom (29.2%) had pyuria. Although the rate was higher than in those with a BMI of <30 kg/m^2, the difference did not reach statistical significance. A possible reason for the discrepancy between our findings and the previous studies may be due to racial differences and different obesity criteria [29]. Prepregnancy obesity has been reported to be associated with hypertensive disorders complicating pregnancy, cesarean delivery, macrosomia and large-for-gestational-age infants. [30] Previous study also reported women with prepregnancy obesity increased risks of preterm birth and PPROM [31,32]. However, prepregnancy obesity was not a predictor for preterm birth and PPROM in our analysis, which may be due to the small population size in our study cohort.

Advanced age has been reported to be associated with an increased risk of maternal hypertension, diabetes, preterm births, LBW, low Apgar score, still birth, and intrauterine fetal death, especially in women aged over 40 years who are primiparous [30].

Table 4
Multivariate analysis of factors associated with a low Apgar score.

Variable	OR	95% CI	*p*
Pyuria	4.917	1.82–13.38	0.002
Advanced maternal age	3.486	1.11–10.92	0.032

$p < 0.05$ was considered statistically significant.
CI = confidence interval; OR = odds ratio.

Five-minute Apgar scores <7 have been reported to be associated with an increased risk of perinatal mortality and severe neurological morbidity [33]. In our study, we found that a maternal age of 35 years and over was an independent predictor for a low 5-minute Apgar score (<7), however, it was not associated with preterm delivery, PPROM, or LBW. The discrepancy between studies may be due to different age cutoff values, and also because we did not include the effect of parity in our analysis.

This study has several limitations. First, this was a retrospective study with a large referral of high risk pregnant women from local clinics, and therefore we could not adjust for some unexpected confounding factors. Second, bacterial vaginosis is a well-known factor associated with preterm delivery and PPROM [34]; however, this factor was not included in our analysis due to a lack of data. Third, the procedure for urine collection was not standardized, although each woman was shown how to collect clean-voided midstream urine. Fourth, prepregnancy BMI and gestational weight gain were also not available in our study, and they may have been related to LBW and macrosomia [35]. Our study does not report the incidence of asymptomatic bacteriuria detected by urine culture among patients with asymptomatic pyuria by urinalysis.

In conclusion, although urine culture is the gold standard for the diagnosis of UTI or bacteriuria, urinalysis has the benefits of being low cost, and it can also quickly detect pyuria. In the present study, we demonstrated that even asymptomatic pyuria detected by urinalysis was associated with poor perinatal outcomes such as preterm delivery, PPROM, LBW, and lower Apgar scores. Thus urine cultures should be performed when asymptomatic pyuria is detected during first trimester screening, and aggressive antibiotic treatment is mandatory. A prospective randomized controlled trial with more cases and well-controlled confounding factors may be needed to verify our results.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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