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Outcome of Pregnancy Complicated by Asymptomatic Bacteriuria

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Abstract

Objective: To evaluate pregnancy outcome in women with asymptomatic bacteriuria (ASB).

Design: Prospective cohort study.

Setting: The University Teaching Hospital Yaoundé (Cameroon) from May 1st, 2012 to April 30th, 2014.

Population: Fifty two women with (treated) ASB and 156 without ASB were followed up till delivery.

Methods: Data were analyzed using Epi-info 3.5.4. Data of women with ASB were compared to those of women without ASB. Fisher's exact test and t-test were used for comparison. P<0.05 was considered statistically significant. Main outcome measures: Maternal age and parity, bacteria isolated from urine culture and its sensitivity, gestational age (GA) at diagnosis of ASB and at delivery, maternal complication during pregnancy, fetal sex and the birth weight.

Results: The mean GA at diagnosis of ASB was 21.0 ± 7.0 weeks. The main micro-organism isolated was Escherichia coli. The two antibiotics usually efficient were ceftriaxone and amoxicillin-clavulanic acid. There was no significant differences regarding maternal age, parity or the mean GA at delivery in both groups. ASB was associated with preterm birth (RR 2.4) and especially with low birth weight (LBW:<2500 g) (RR 5), especially when diagnosed early in pregnancy (RR 7.4). No case of pre eclampsia or pyelonephritis was observed in the ASB group.

Conclusion: ASB is associated with LBW especially when present early in pregnancy.

Keywords: Asymptomatic bacteriuria; Etiological pathogen isolated; Pregnancy outcome

Introduction

Asymptomatic bacteriuria (ASB) is defined as the presence of ≥105 bacteria of the same species per ml of urine in a symptomless patient. ASB is the most frequent infection worldwide [1]. It is also a frequent event during pregnancy with a prevalence varying between 2% and 10% worldwide [2]. The risk of developing ASB in pregnancy is low (2.2%) in the first trimester, highest in the second trimester (69.8%) while 28% occur in the third trimester [3].

Pathogens involved in ASB are usually enteric bacteria meaning that ASB results mainly from contamination from the digestive system from the anal area. The most common pathogen responsible is uropathogenic *Escherichia coli* [4] which, by means of its adhesins (the pili it contains), has the capacity to adhere to the epithelial cells of the urinary tract mucosa. It multiplies before invading the upper urinary tract [1,5].

Risk factors for ASB in pregnancy include diabetes mellitus, multiple pregnancies, urinary tract malformation, low socioeconomic status, multiparity, past history of urinary tract infections and sickle cell diseases [6]. Sexual activity is associated with an increased risk of ASB because during sexual intercourse, bacteria are pushed into the urethra [7,8], while micturition after sexual intercourse is a protective factor [9]. ASB seems to be rare in teenagers [3].

If left untreated, as many as 30-50% of women will develop acute pyelonephritis [2]. When screening for ASB is done between 12 and 16 weeks gestation, it will identify 70-80% of women who will present ASB during pregnancy [3,10].

ASB seems to be associated with increased risk of pre-eclampsia, premature labor, premature rupture of membranes, intra-uterine growth retardation, low birth weight (LBW) [11]. Hence, ASB should be diagnosed and treated earlier. Diagnosis of ASB is done through urine culture. Antibiotic treatment may reduce the adverse effects of ASB. Given that Cameroon is a low income country where many women are of low socioeconomic status, we expect ASB to be more frequent and more severe in our environment. Hence, this study aimed at evaluating ASB incidence, risk factors and pregnancy outcomes in women with ASB.

Materials and Methods

This prospective cohort study was conducted in the maternity of the University Teaching Hospital Yaoundé, Cameroon, from May 1st, 2012 to April 30th, 2014. All women with or without ASB diagnosed at the first consultation were recruited. Diagnosis of ASB was done between 12 and 38 weeks gestation by the presence of ≥10^5 colony-

forming units of a single organism per milliliter of clean-catch midstream urine specimen in a symptomless patient.

Before collecting urine, the vulva was cleaned thrice from front to back with gauze soaked with normal saline, then a clean-catch midstream urine sample was collected into a wide mouthed sterile capped container. The urine sample was cultured on blood agar and Cysteine Lactose Electrolyte deficient (CLED) agar. Inoculated plates were incubated at 37°C aerobically overnight, the plates read and the bacteria identified based on their growth characteristics, the Gram stain, the biochemical and sugar fermentation tests. The biochemical tests used were the indole test for lactose fermenting bacteria such as *Escherichia coli* (*E coli*) and *Klebsiella*, and coagulase test to differentiate *Staphylococcus aureus* from coagulase negative *staphylococcus*. Sensitivity was tested using Kirby-Bauer disc diffusion test. The isolates were tested against different antibiotics. Women with ASB received antibiotic treatment for a duration of 8 days. The urine culture was repeated one month after complete treatment to assess recurrence.

For each woman with ASB recruited, three women without ASB who did not take antibiotics within the previous two weeks were recruited. Women without ASB who took oral antibiotics within the preceding two weeks were excluded from the group without ASB because they could have been involuntarily treated for ASB. Women who were lost during follow up were also excluded. All the women had routine antenatal follow-up till delivery. An informed consent was obtained from each woman. This study was approved by the institutional ethics committee.

Variables recorded on a pre-established and pretested questionnaire by the principal investigator included parity, maternal age at delivery, gestational age at diagnosis of ASB and at delivery (validated by an ultrasound scan performed before 20 weeks gestation), maternal hemoglobin electrophoresis, the HIV status, the bacteria identified at urine culture and its sensitivity to antimicrobial agents, the fetal sex, birth weight and maternal complications.

Variables		Group with ASB	Group without ASB	P value
Number of women		52	156	
Maternal age (year)	Mean ± SD (range)	28.8 ± 5.3 (18-43)	28.4 ± 5.0 (17-44)	0.62
	<20	1 (1.9%)	6 (3.8%)	
	20-24	7 (13.5%)	30 (19.2%)	
	25-29	24 (46.1%)	57 (36.5%)	
	30-34	13 (25%)	46 (29.5%)	
	≥35	7 (13.5%)	17 (10.9%)	
Parity	Mean ± SD (range)	1.4 ± 1.6 (0-6)	1.4 ± 1.5 (0-7)	1
	≤1	32 (61.5%)	96 (61.5%)	
	≥2	20 (38.5%)	60 (38.5%)	
GA at diagnosis(week)	Mean ± SD (range)	21.0 ± 7.0 weeks (12-37)	-	-
	16-Dec	14 (26.9%)	-	
	17-37	38 (73.1%)	-	
GA at delivery(week)	Mean ± SD (range)	39.1 ± 1.6 (36-42)	39.2 ± 1.6 (35-42)	0.69
	<37	4 (7.7%)	5 (3.2%)	
	≥37	48 (92.3%)	151 (96.8%)	
BW (in gram)	Mean ± SD (range)	3313.5 ± 486.2 (2300-4117)	3327.3 ± 456.3 (2200-4824)	0.85
	<2500	5 (9.6%)	3 (1.9%)	
	≥2500	47 (90.4%)	153 (98.1%)	
ASB: Asymptomatic bacteriuria, GA: Gestational age, BW: Birth weight				

Table 1: Distribution of demographic and obstetrical variables among both groups.

Sample size was calculated as requiring at least 42 women with ASB [12]. To avoid selection bias of women without ASB, we decided to recruit three women without ASB for each woman with ASB. Data were analyzed using Epi info 3.5.4. Data of women with ASB were compared to those of women without ASB. Fisher's exact test was used to compare categorical variables and t-test to compare continuous variables. We used relative risks with their 95% confidence intervals (CIs) to present the comparison between the two groups.

P<0.05 was considered statistically significant. The results are presented as mean ± standard deviation (SD) for quantitative data and frequencies for qualitative data.

Results

A total of 719 pregnant women were screened, 56 of them had ASB, giving an incidence of 7.8%. Four women with ASB and 14 controls were lost during follow-up. Each control lost was replaced by the woman without ASB who immediately followed her on the consultation list. The variables of the remaining 52 women with ASB and the 156 without ASB followed up till delivery were analyzed. Only 26.9% of ASB was diagnosed between 12 and 16 weeks. Data are shown in Table 1.

Married women were observed in 59.6% in the ASB group and 65.7% in the group without ASB. Hemoglobin electrophoresis showed that 8/52 women had AS hemoglobin as against 16/156 in the group without ASB (RR 1.3, 95%CI 0.7-2.6, P=0.45) while 4/52 women and 12/156 in the group without ASB were HIV positive (RR 1, 95%CI 0.4-2.4, P=1). The micro-organisms commonly found were *E coli* (30 cases or 57.7%) and *Staphylococcus aureus* (10 cases or 19.2%) (Table 2).

The sensitivity of micro-organisms to antibiotics revealed that the two most common efficient antibiotics were ceftriaxone and amoxicillinclavulanic acid (Table 3). One month after treatment, all women were negative for ASB.

Bacteria	Number	%
Escherichia coli	30	57.7
Staphylococcus aureus	10	19.2
Klebsiella species	6	11.5
Staphylococcus epidermitis	2	3.8
Staphylococcus saprophyticus	1	1.9
Coagulase negative staphylococcus	1	1.9
Proteus mirabilis	1	1.9
Group B streptococcus	1	1.9
Total	52	100
ASB: Asymptomatic bacteriuria		

Table 2: Distribution of micro-organisms cultured in the ASB group

No case of pre-eclampsia occurred in the ASB group, but two women developed preeclampsia in the group without ASB. No woman developed neither pyelonephritis nor sepsis, acute respiratory distress syndrome or death in neither group.

Bacteria	Sensitive to*			
	Ceftriaxone N (%)	AmoxiClav† N (%)	Cefuroxime N (%)	Cefixime N (%)
Escherichia coli (n=30)	14 (46.7)	12 (40.0)	11 (36.7)	5 (16.7)
Staphylococcus aureus (n=10)	5 (50)	4 (40)	4 (40)	0 (0)
Klebsiella spp (n=6)	3 (50)	0 (0)	2 (33.3)	0 (0)
Staphylococcus epidermitis (n=2)	1 (50)	2 (100)	1 (50)	0 (0)
Staphylococcus saprophyticus (n=1)	0 (0)	1 (100)	0 (0)	0 (0)
Coagulase negative staphylococcus (n=1)	0 (0)	0 (0)	1 (100)	0 (0)
Proteus mirabilis (n=1)	1 (100)	0 (0)	0 (0)	0 (0)
Group B *streptococcus* (n=1)	0 (0)	1 (100)	1 (100)	0 (0)
Total =52 (100%)	24 (46.1)	20 (38.5)	20 (38.5)	5 (9.6)
*Some bacteria were sensitive to many antibiotics. †Amoxicillin + Clavulanic acid				

Table 3: Sensitivity of bacteria to commonly used antibiotics

Preterm birth (<37 completed weeks of gestation) occurred frequently (7.7%) in the ASB group (RR 2.4, 95%CI 0.6-8.6, P=0.23) (Table 1). When we took into consideration the moment of diagnosis of ASB, preterm birth occurred in 1/14 cases in the early detected ASB group as against 5/156 in the group without ASB (RR 2.2, 95%CI 0.2-17.7, P=0.40) and in 3/38 cases in the late detected ASB group as against 5/156 in the group without ASB (RR 2.4, 95%CI 0.6-9.8, P=0.35).

LBW (<2500 g at delivery) was frequently observed in the ASB group (9.6%) (RR 5, 95%CI 1.2-20.2, P=0.024) (Table 1). When we compared birth weight according to gestational age at diagnosis, we found that LBW was noticed in 3/38 (7.9%) in the late detected ASB group and in 3/156 (1.9%) in the group without ASB (RR 4.1, 95%CI 0.8-19.5, P=0.09), while it was noticed in 2/14 (14.3%) in the early detected ASB group and in 3/156 (1.9%) in the group without ASB (RR 7.4, 95%CI 1.3-40.8, P=0.054).

In the ASB group, 27/52 fetuses (51.9%) were female compared to 78/156 (50%) in the group without ASB.

Discussion

Our prevalence of ASB (7.8%) is within the range found worldwide which varies between 2 and 11% [13,14]. This might show that the prevalence of ASB is less influenced by the country income status. Some authors found rates as high as 18.8% [15].

The most affected maternal age range was between 25 and 29 years as observed by other authors [3,14]. ASB was rarely found among teenagers [3], as in our series. ASB might be favored by sexual activity since there might exist increased sexual activity in this 25 to 29 age group. Sexual activity has been shown to favor ASB because during sexual intercourse, bacteria are pushed into the urethra [7,8].

We also found that women of low parity (≤1) were tested more positive for ASB. This might not be a risk factor per se, but might be associated with young age, since low parity is usually associated with younger age. The commonest bacteria found in our series was *E. coli* in accordance with other studies [4,14]. This may be due to its virulence and especially its increased adhesive ability. Indeed, uropathogenic *E. coli* contains adhesins that permit it to adhere to uroepithelial cells, hence, preventing it from urine washing [1,5]. At this moment, *E. coli* multiplication and tissue invasion occur. *Staphylococcus aureus* was the second bacteria frequently responsible in our series, contrary to other studies which found that was the first bacteria isolated [15].

The three antibiotics that were usually efficient in treating ASB were ceftriaxone, amoxicillinclavulanic acid and cefuroxime. As concerns maternal complications of ASB, we had no case of pyelonephritis, contrarily to other studies which found rates of 1-4% of acute pyelonephritis among women treated for ASB [16]. Some authors found high risk of preeclampsia among women with ASB and thought that the increased maternal cytokines observed in ASB may affect vascular endothelial function and may lead to the subsequent development of pre-eclampsia [17]. We had no case of pre-eclampsia in women with ASB in our series.

Contrarily, we found an increased risk of preterm birth (RR 2.4) among women with ASB, though not statistically significant. This has also been documented by others [11]. Proinflammatory cytokines secreted by maternal or fetal macrophages in response to bacterial endotoxins may initiate labor in women with ASB, as suggested by some researchers [18].

Antibiotic treatment may stop or limit this inflammatory process [2,11]. Antibiotic treatment should follow the standard 7-day regimen which is more efficient than the one-day regimen [19]. Our rate of preterm delivery in women with ASB (7.7%) is lower than the reported rate of 27% in case ASB being left untreated [14]. Hence, ASB should be screened and treated early in pregnancy. Studies found no statistically significant difference in the recurrence of asymptomatic bacteriuria rate between treated group and controls [2]. In our ASB group, no recurrence was observed one month after treatment. This might be explained in our study by the 8-day regimen or the fact that once ASB was diagnosed and treated, counseling was done on the need of increasing oral fluid intake and on micturition after sexual intercourse given that this protective effect has been proved [9]. Increased oral fluid intake increases micturition frequency or volume which may help in washing bacteria from the urinary tract.

Moreover, we observed that women with ASB had increased risk of LBW (RR 5.0) in accordance with other studies [11]. The explanation of this is not well known. Some authors think that ASB is not directly associated with LBW, but rather, might be present with other bacteria in the vagina or cervix which could be associated with subclinical chorioamnionitis [20]. We think that eradication of bacteria present in the urine may stop or only reduce the inflammatory process. Furthermore, in case of eradication of the bacteria present in the urine only, the bacteria still present on the cervix or in the amniotic fluid (in case it is not sensitive to the antibiotics used) may sustain the inflammatory process which may lead to preterm birth or LBW. These two hypotheses might explain why treatment of ASB is only associated with a reduction of LBW and preterm birth rate. Further studies should be conducted to confirm these hypotheses.

LBW rate was higher for women diagnosed early with ASB (RR 7.4) than for those diagnosed later (RR 4.1). This might show that ASB present early in pregnancy, even when treated, is associated with an increased risk of LBW. This might be explained by the hypotheses above mentioned. This is contrary to what was found elsewhere, where early detection and treatment was associated with similar outcomes as in women without ASB [11].

The limitations of our study are that some confounding factors such as low economic status, passive smoking, anemia or placental anomalies might have affected the frequency of LBW in our series.

Conclusion

ASB is frequent in pregnancy and is associated with low birth weight especially when it is present early in pregnancy. Therefore, all pregnant women should be screened for ASB early enough and treated in order to reduce the risk of adverse effects.

Footnote

The formula for calculating sample size was: $N = 2\times(Z\alpha+Z\beta / P0-P1)^2 \times P\times(1-P)$ where $Z\alpha = 1.28$ corresponding to a type I error of 10%, $Z\beta = 0.84$ corresponding to a type II error of 0.2 or a power or 80%, P0 the prevalence of low birth weight (LBW) in women with ASB (15%), P1 the prevalence of LBW in women without ASB (2%) and P is (P0+P1)/2.

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