
OBSTETRICS

The Prevalence of Bacterial Vaginosis in Asymptomatic Pregnant Women during Early Third Trimester and the Pregnancy Complications

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ABSTRACT

Objectives: To investigate the prevalence of bacterial vaginosis (BV) in asymptomatic pregnant women during early-third trimester and to compare the pregnancy complications between pregnant women with and without BV.

Materials and Methods: A total of 270 asymptomatic pregnant women at GA 28-32 weeks without history of preterm birth (PB) or cervical surgery were screened for BV, along with other vaginal infections, using gram stain. Nugent criteria was used to categorize vaginal smears into no BV (score 0-3), intermediate flora (IF, score 4-6) and BV (score 7-10). Fifteen weeks later, their medical records were reviewed. Outcomes of interest were premature rupture of membranes (PROM), preterm birth <37 weeks (PB) and birth weight <2,500 grams (LBW).

Results: From 270 participants, 233 who delivered at Siriraj hospital were eligible for the study. The prevalence of BV, vaginal candidiasis (VC) and IF were 19.3%, 21% and 36.5%, respectively. None had trichomoniasis or gonococcal infection. One of BV cases had chorioamnionitis and none of all participants had post-partum infection. Multivariate analysis showed the increasing trend of pregnancy complications: PROM (IF 1.6, 95% CI 0.6-4.5; BV 2.2, 95% CI 0.8-6.2, $p=0.339$), PB (IF 1.3, 95% CI 0.3-5.1; BV 2.3, 95% CI 0.6-9.4, $p=0.489$) and LBW (IF 1.4, 95% CI 0.5-4.1; BV 1.5, 95% CI 0.5-4.9, $p=0.761$).

Conclusion: BV during GA28-32 weeks in asymptomatic Thai pregnant women was prevalent at 19.3% and tended to increase in pregnancy complications, including premature rupture of membranes, preterm birth and low birth weight.

Keywords: bacterial vaginosis, intermediate flora, low birth weight, preterm birth, PROM

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ความซูกของภาวะ Bacterial vaginosis ในหญิงตั้งครรภ์ที่ไม่มีอาการช่วงไตรมาสสาม ตอนต้น และผลต่อการตั้งครรภ์

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความซูกของภาวะ bacterial vaginosis ในหญิงตั้งครรภ์ที่ไม่มีอาการช่วงไตรมาสสามตอนต้น และเปรียบเทียบผลแทรกซ้อนไม่พึงประสงค์ของการตั้งครรภ์ ระหว่างกลุ่มที่มีและไม่มีภาวะ bacterial vaginosis

วัสดุและวิธีการ: ศึกษาเพื่อหาความซูกของภาวะ bacterial vaginosis ในหญิงตั้งครรภ์ที่ไม่มีอาการผิดปกติ อายุครรภ์ระหว่าง 28 ถึง 32 สัปดาห์ จำนวน 270 ราย ที่ไม่มีประวัติคลอดก่อนกำหนด และประวัติผ่าตัดปากมดลูก โดยการตรวจภาวะ bacterial vaginosis จาก vaginal swabs โดยใช้ Nugent criteria ในการวินิจฉัย และคัดแยกผู้ป่วยเป็นกลุ่ม bacterial vaginosis (คะแนน 0-3) กลุ่ม intermediate flora (คะแนน 4-6) กลุ่มปกติ (คะแนน 7-10) และทำการเก็บข้อมูลจากเวชระเบียนที่ 15 สัปดาห์ หลังจากเข้าร่วมงานวิจัยเพื่อศึกษาถึงความสัมพันธ์ของภาวะต่างๆ กับผลแทรกซ้อนไม่พึงประสงค์ของการตั้งครรภ์ที่ต้องการศึกษา ได้แก่ ภาวะน้ำเดินก่อนเจ็บครรภ์คลอด ภาวะคลอดก่อนกำหนดที่อายุครรภ์น้อยกว่า 37 สัปดาห์ และภาวะน้ำหนักทารกแรกเกิดน้อยกว่า 2,500 กรัม

ผลการศึกษา: จากจำนวนผู้เข้าร่วมวิจัย 270 ราย มีทั้งสิ้น 233 ราย ที่คลอด ณ โรงพยาบาลศิริราช พบรความซูกของภาวะ bacterial vaginosis ร้อยละ 19.3 ภาวะ intermediate flora ร้อยละ 36.5 และภาวะเชื้อราในช่องคลอดร้อยละ 21 ในกลุ่มที่มีภาวะ bacterial vaginosis พบรผู้ป่วยที่วินิจฉัย chorioamnionitis 1 ราย จากการศึกษาไม่พบรการติดเชื้อ trichomoniasis การติดเชื้อ gonococcus และ postpartum infection ในกลุ่มที่มีภาวะ bacterial vaginosis มีแนวโน้มที่จะเกิดภาวะไม่พึงประสงค์ระหว่างการตั้งครรภ์สูงกว่ากลุ่ม intermediate flora และกลุ่มเปรียบเทียบตามลำดับ โดยภาวะน้ำเดินก่อนการเจ็บครรภ์คลอด (aOR 2.2 VS. 1.6, $p = 0.339$) ภาวะคลอดก่อนกำหนด (aOR 2.3 VS. 1.3, $p = 0.489$) และภาวะทารกน้ำหนักทารกแรกเกิดน้อยกว่า 2,500 กรัม (aOR 1.5 VS. 1.4, $p = 0.761$)

สรุป: ความซูกของภาวะ bacterial vaginosis ในหญิงตั้งครรภ์ที่ไม่มีอาการช่วงไตรมาสสามตอนต้นคือ ร้อยละ 19.3 เมื่อเปรียบเทียบกับกลุ่มปกติ พบร่วงคลอดก่อนกำหนดที่มีภาวะ bacterial vaginosis และ intermediate flora มีแนวโน้มที่จะเพิ่มความเสี่ยงต่อผลที่ไม่พึงประสงค์ในการตั้งครรภ์ ได้แก่ ภาวะน้ำเดินก่อนเจ็บครรภ์คลอด ภาวะคลอดก่อนกำหนดที่อายุครรภ์น้อยกว่า 37 สัปดาห์ และภาวะน้ำหนักทารกแรกเกิดน้อยกว่า 2,500 กรัม

คำสำคัญ: ภาวะ bacterial vaginosis, ภาวะ intermediate flora, ภาวะน้ำเดินก่อนเจ็บครรภ์คลอด, ภาวะคลอดก่อนกำหนดที่อายุครรภ์น้อยกว่า 37 สัปดาห์ และภาวะน้ำหนักทารกแรกเกิดน้อยกว่า 2,500 กรัม

Introduction

Bacterial vaginosis (BV) during pregnancy is very common, accounting for 15.6-26.0%⁽¹⁻⁶⁾, and associates with many adverse pregnancy outcomes such as premature rupture of membranes (PROM), preterm birth (PB), chorioamnionitis, low birth weight (LBW) and post-partum infection^(2, 3, 7). The imbalance of vaginal microbes may produce inflammatory substance accounting for those outcomes. Alteration in the integrity of amniotic membranes following the inflammatory process may lead to the leakage of amniotic fluid and result in the perinatal morbidity and mortality⁽⁸⁾.

Despite its high prevalence during pregnancy and association with adverse pregnancy outcomes, there is no consensus for the universal screening during antenatal care⁽⁹⁾. There has been controversy on the benefits of screening and treatment of lower genital tract infection for preventing PB^(10, 11). However, most of the studies focused on gestational age (GA) less than 24 weeks. Meis et al. showed that BV at GA 28 weeks significantly increased the incidence of PB up to 84% and had higher predictability than BV at GA 24 weeks⁽¹²⁾. Thus, the present study aimed to examine the prevalence of BV in asymptomatic pregnant women during the early third-trimester (GA 28-32 weeks) and the pregnancy outcomes.

Materials and Methods

The prospective observational study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University between July 2015 and July 2016. Ethical approval was granted by the Siriraj Institutional Review Board (COA. 283/2558).

Participants

Consecutive pregnant women who attended the antenatal care (ANC) clinic at Siriraj Hospital were invited to participate in the study. Inclusion criteria included age 18-35 years, singleton, GA 28-32 weeks, normal routine serologic screening (for human immunodeficiency virus infection, syphilis and hepatitis

B), no abnormal vaginal discharge or vaginal pruritus, those without risk factors for PB such as previous cervical conization and previous PB. Exclusion criteria were not willing to give the information about pregnancy outcomes, not consent for pelvic examination and delivery outside Siriraj Hospital.

All participants had at least one ultrasonographic scan for the exact GA. After obtaining the informed consent, the participants' demographic data were recorded. Then, they were asked to be in lithotomy position for high vaginal swabs which were immediately smeared on labeled slides and air-dried.

Gram stain of the smears

The gram staining of the smears was performed by a trained technician. The slides were then examined by other two skilled technicians who did not know each other and had at least five-year experience. One was a cytologist and another was a microbiologist. BV was diagnosed by using Nugent criteria⁽¹³⁾ which was a scoring tool on three categories of the vaginal flora including *Lactobacillus* spp., *Gardnerella*/ *Bacteroides* spp. and curved gram variable rods. The score ranged from 0-10: scores 0-3 was graded as normal, scores 4-6 was graded as intermediate flora (IF) and scores 7-10 was graded as BV. Scores from both technicians were combined and the averaged score was used for the final interpretation. In addition, the technicians were asked to look for *N. gonorrhoea* (gram-negative diplococccic bacteria), trichomoniasis (flagellated protozoa) and fungal infection (pseudohyphae). According to Guideline by the Society of Obstetricians and Gynaecologists, Canada (SOGC) 2008⁽⁹⁾, no medications were provided for BV and intermediate flora for our participants as they were asymptomatic.

Adverse pregnancy outcomes

Fifteen weeks after the enrollment, the medical records of the participants who delivered at Siriraj Hospital were reviewed. The pregnancy complications of interest included PROM, chorioamnionitis, PB, LBW and post-partum infection. PROM was defined as leakage of amniotic fluid at least 1 hour prior to onset

of true labor pain. PB was defined as delivery before 37 completed weeks of gestation. Chorioamnionitis was defined as maternal temperature $\geq 37.8^{\circ}\text{C}$ with one or more clinical signs, including fetal tachycardia, maternal tachycardia, uterine tenderness and foul smell amniotic fluid. Low birth weight defined as a birth weight less than 2500 grams. Postpartum infection referred to postpartum endometritis (abnormal vaginal discharge/ prolonged lochia rubra and uterine tenderness) and cesarean wound infections.

Statistical analysis

The sample size was calculated by using the prevalence of BV in American pregnant women (prevalence 16.0%)⁽⁵⁾ in an equation: $N = [Z^2 \cdot \alpha/2 \cdot P(1-P)] / e^2$. The required sample size was 207 and the total sample size was 270 when 30% loss was included.

Stata version 12.1 (StataCorp LP, Texas, USA) was used for the analysis. To describe participants' characteristics, $n(\%)$ and mean \pm S.D. were used. Chi square test, Fisher's exact test and T-test were used for the comparison. Logistic regression analysis was used to explore the association between categories of vaginal flora and adverse pregnancy outcomes. P-value < 0.05 was considered statistically significant.

Results

From 270 pregnant women, 233 delivered at Siriraj Hospital and were eligible for the study. Based on Nugent criteria, the prevalence of BV and intermediate flora were 19.3% and 36.5%, respectively. Around 20% of the smears contained pseudohyphae which was suggestive of fungal infection. No gonococcal infection and trichomoniasis was detected.

The participants were 27.4 ± 5.1 year-old and had body mass index (BMI) at $25.8 \pm 4.4 \text{ kg/m}^2$. The GA at examination was around 30 weeks. Almost all of them graduated from high school. Around one fourth stopped working during pregnancy and one half was primiparous. Primiparity was more common in BV group (64.4% vs. 47.3%, $p=0.039$). Around 10% of the participants underwent curettage due to previous miscarriage. Only one participant was a current

smoker who belonged to non-BV group. Eight women (3.4%) consumed alcoholic drink during pregnancy. Three-fourths of the participants remained sexually active during pregnancy and reported recent intercourse (Table 1).

Past history of sexually transmitted infections (STIs) was quite high in that 17 women (7.3%) had herpes genitalis, four women (1.7%) had pelvic inflammatory disease (PID), two women had condyloma accuminata (0.9%) and one woman had gonococcal infection (0.4%). The lag period from the screening to delivery was comparable between groups: BV at 8.3 ± 2.0 weeks and non-BV at 8.3 ± 1.9 weeks.

On average, the delivery occurred at GA 38.4 ± 1.3 weeks. Elective Caesarean section was set in 40 cases (17.2%), including 34 women with previous caesarean section and 6 women with non-vertex presentation. Emergency Caesarean sections were indicated with cephalo-pelvic disproportion (23/233, 9.9%) and non-reassuring fetal heart rate pattern (17/233, 7.3%). Birth weight was $3,025 \pm 418$ grams. Apgar scores less than 7 at one minute was found in 12 participants (5.2%) but none of the infants had Apgar score less than 7 at 5 minutes. The pregnancy complications included PROM in 27 women (11.6%), PB in 13 women (5.6%) and LBW in 21 women (9.0%). We found no deliveries before GA 34 weeks and no post-partum infection. Only one woman who had BV had chorioamnionitis.

Table 2 shows logistic regression to demonstrate the association between Nugent scoring groups and the pregnancy complications. When adjusting to age, parity, GA at screening and fungal infection, the greater disturbance to vaginal ecosystem tended to increase PROM (IF 1.6, 95% CI 0.6-4.5; BV 2.2, 95% CI 0.8-6.2, $p=0.339$), PB (IF 1.3, 95% CI 0.3-5.1; BV 2.3, 95% CI 0.6-9.4, $p=0.489$) and LBW (IF 1.4, 95% CI 0.5-4.1; BV 1.5, 95% CI 0.5-4.9, $p=0.761$) although there was no statistical significance. There was no association between fungal infection and the pregnancy complications (PROM 0.8, 95% CI 0.3-2.3, $p=0.734$; PB 0.3, 95% CI 0.04-2.4, $p=0.178$; LBW 0.9, 95% CI 0.3-2.7, $p=0.813$).

Table 1. Characteristics of the participants and pregnancy outcomes.

	Total (n=233)	Bacterial vaginosis (n=45)	No bacterial vaginosis (n=188)	p value
Age	27.4 ± 5.1	27.2 ± 5.3	27.5 ± 5.0	0.713
BMI	25.8 ± 4.4	25.3 ± 3.6	25.9 ± 4.5	0.394
Education ≥ high school	225 (96.6)	44 (97.8)	181 (96.3)	1.000
No working/ Housewives	64 (27.5)	12 (26.7)	52 (27.7)	0.893
Primiparity	118 (50.6)	29 (64.4)	89 (47.3)	0.039
GA at exam	29.8 ± 1.3	29.2 ± 1.5	30 ± 1.5	0.095
Previous curettage	23 (9.9)	2 (4.4)	21 (11.2)	0.265
Alcohol consumption	8 (3.4)	1 (2.2)	7 (3.7)	1.000
SI during pregnancy	166 (71.2)	33 (73.3)	133 (70.7)	0.730
History of STDs				
Herpes genitalis	17 (7.3)	3 (6.7)	14 (7.5)	1.000
Gonorrhea	1 (0.43)	0	1 (0.5)	1.000
Genital warts	2 (0.9)	1 (2.2)	1 (0.5)	0.350
PID	4 (1.7)	1 (2.2)	3 (1.6)	0.579
Fungal infection	49 (21.0)	6 (13.3)	43 (22.9)	0.158
Pregnancy outcomes				
GA at delivery	38.4 ± 1.3	38.1 ± 1.4	38.5 ± 1.2	0.072
Birthwieght	3,025 ± 418	2,980 ± 384	3,036 ± 426	0.414
Apgar score < 7 at 1 minute	12 (5.2)	3 (6.7)	9 (4.8)	0.608

Data presented in n (%) and mean ± S.D.

BMI = body mass index, GA = gestational age, PID = pelvic inflammatory disease, SI = sexual intercourse, STDs = sexually transmitted diseases

Table 2. Association between intermediate flora/ bacterial vaginosis and pregnancy complications.

		N (%)	cOR	p value	aOR*	p value
Premature rupture of membranes	No BV (n=103)	9 (8.7)	Reference	0.286	Reference	0.339
	Intermediate (n=85)	10 (11.8)	1.4 (0.5-3.6)		1.6 (0.6-4.5)	
	BV (n=45)	8 (17.8)	2.3 (0.8-6.3)		2.2 (0.8-6.2)	
Birth before 37 weeks	No BV (n=103)	5 (4.9)	Reference	0.532	Reference	0.489
	Intermediate (n=85)	4 (4.7)	1.0 (0.3-3.7)		1.3 (0.3-5.1)	
	BV (n=45)	4 (8.9)	1.9 (0.5-7.5)		2.3 (0.6-9.4)	

Table 2. Association between intermediate flora/ bacterial vaginosis and pregnancy complications. (Cont.)

		N (%)	cOR	p value	aOR*	p value
Low birth weight (< 2,500 grams)	No BV (n=103)	8 (7.8)	Reference	0.797	Reference	0.761
	Intermediate (n=85)	8 (9.4)	1.2 (0.4-3.4)		1.4(0.5-4.1)	
	BV (n=45)	5 (11.1)	1.5 (0.5-4.8)		1.5 (0.5-4.9)	

aOR = adjusted odd ratio, BV = bacterial vaginosis, cOR= crude odd ratio

aOR* adjusting for age, parity, GA at screening and fungal infection

Discussion

This prospective study showed that altered vaginal flora was found in around half of asymptomatic pregnant women during GA 28-32 weeks and one-fifth met the criteria for BV. There was a tendency to increase PROM, PB and LBW among them. We found one case of chorioamnionitis who had BV at the screening. None of the participants demonstrated post-partum infection. Fungal infection was found in 21.0% of the participants and showed no association with BV or any adverse pregnancy outcomes. Neither gonococcal infection nor trichomoniasis was identified in the study population.

Concordant to previous studies which used gram staining as a diagnostic tool and demonstrated the prevalence of BV during pregnancy at 16-26%⁽¹⁻⁵⁾, we found that of BV at 19.3%. Three previous studies included pregnant women in a wide range of GA (any GA^(1, 3) or GA 14-36 weeks⁽²⁾) while two studies focused on pregnant women with GA lower than our study (GA 8-17 weeks⁽⁴⁾ and GA 23-26 weeks⁽⁵⁾). Hillier⁽⁵⁾ showed the prevalence of BV in asymptomatic nationality pregnant women at 16% while another study in general population reported the prevalence of BV at as high as 26%⁽²⁾. Since this study focused on asymptomatic cases, this may imply the higher prevalence and impact of BV in general population of Thai pregnant women.

Gram staining is a reliable diagnostic tool for BV with higher accuracy⁽¹⁴⁾ and higher likelihood ratio for PB⁽¹⁵⁾ than clinical criteria (Amsel's criteria). Nugent scoring system was used in the present study because it could categorize vaginal smears into three groups: no

BV, IF and BV⁽¹³⁾. IF should be one of the paramount concerns. A systematic review showed that treating IF together with BV in women with GA below 20 weeks could reduce the incidence of PB by 47%⁽¹⁶⁾. However, IF per se was not homogeneous. A study in Australian women during GA 10-16 weeks demonstrated that IF with lactobacilli had three times lower the incidence of PB than that without⁽¹⁷⁾. We found that, with no statistical significance, it tended to increase the pregnancy complications. This association seemed to be more pronounced among women with BV.

Previous studies in American⁽⁵⁾, Danish⁽³⁾, Finnish⁽⁴⁾, Nigeria⁽²⁾ pregnant women have shown BV increased PROM 1.1-6.8 times, PB 1.5-6.9 times and LBW 1.5-3.2 times. Despite the non-statistical significance, we found a similar trend. However, those studies on the linkage between BV and pregnancy outcomes focused on pregnant women before GA 26 weeks^(4, 5) according to the hypothesis that initiation of inflammatory process in early pregnancy might gradually impair cervical strength. Our target GA was 28-32 weeks because some evidence showed that recurrence of BV after GA 24 weeks during the same pregnancy enhanced the incidence of PB⁽¹²⁾. Additionally, a new episode of BV at GA 28 weeks had even higher predictability of the undesirable outcome⁽¹²⁾. Whether or not treating BV during GA 28-32 weeks is beneficial in terms of preventing PB remains to be answered.

A systematic review on screening and treatment of BV, trichomoniasis and fungal infection before GA 20 weeks showed the significant reduction in PB, LBW and

very low birth weight⁽¹⁰⁾. On the contrary, another recent systematic review showed that there was no benefit of treating BV neither with metronidazole nor clindamycin to prevent PB⁽¹¹⁾. Compatible with a large RCT in Australia⁽¹⁸⁾, the discrepancy between the two studies might be explained by fungal infection and trichomoniasis. In addition, the repeated episode of fungal infection increased PB and LBW⁽¹⁹⁾. Fungal infection was prevalent in our study population, at around 20%. This was paralleled to the findings in American⁽¹²⁾, Finnish⁽²⁰⁾ and Thai⁽⁶⁾ pregnant women.

Primiparity was significantly more common in women without BV. The disturbance of vaginal ecosystem occurs every time pregnancy takes place. Despite its reversible physiological changes of pregnancy, BV might recur more easily. Accordingly, parity and fungal infection, as well as age and GA at examination, were included in the logistic model and appeared to enhance the association between BV and pregnancy complications. Challenging to the practice guideline that treatment of BV in asymptomatic women is not recommended; we demonstrated the increasing trend of pregnancy complications among this population during GA 28-32 weeks. In order to minimize PB; further studies are required.

The strengths of the present study were that we excluded women with established risk factor of PB such as multiple gestations, previous PB and cervical conization. Only low-risk pregnant women were included to demonstrate the effect of BV on pregnancy complications. The diagnostic tool of BV used in the present study was highly accurate. There were also limitations in that the sample size was calculated for the study of prevalence of BV. To detect the difference of adverse pregnancy outcomes, a larger sample size is required. And since we only included asymptomatic women, application was limited to low-risk women without miscarriage prior to GA 28 weeks.

Conclusion

BV during GA 28-32 weeks in asymptomatic pregnant women was prevalent at 19.3% and tended to increase in adverse pregnancy outcomes, including

premature rupture of membranes, preterm birth and low birth weight; however, no statistical significant was demonstrated.

Potential conflicts of interest

The authors declare no conflict of interest.

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