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Screening of vulvovaginal infections during pregnancy in resource constrained settings: Implications on preterm delivery

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Abstract The present study was undertaken to evaluate the efficacy of clinical and microbiological investigations available in limited resource settings for an effective diagnosis of vaginal infections/abnormal vaginal microbiota among pregnant women. As an outcome of the study we intended to find the association of various vaginal infections during pregnancy with preterm delivery. Pregnant women presenting for routine antenatal care at an antenatal clinic in south India were enrolled in the study. Each participant underwent clinical and microbiological examinations for the diagnosis of vaginal infections such as bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) and trichomoniasis. In addition, Gram's stained high-vaginal smears were evaluated for the presence of partial BV and vaginitis. Diagnostic accuracies of clinical diagnosis for the aforementioned infections was determined in comparison

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with gold standard microbiological diagnosis. Proportion of women with vulvovaginal infections were estimated using descriptive statistics and incidence risk ratio for preterm delivery with each form of the infection was estimated using univariate analysis. A total of 790 pregnant women were recruited in the study. Positive predictive values of clinical diagnosis for BV, VVC and Trichomoniasis in comparison with reference method were 72.7, 33.5 and 37.6% respectively. Partial BV (3.2%) and vaginitis due to mixed bacterial etiology (9.4%) were per exclusionem diagnosed using the microbiological smear examination. Microbiological diagnosis of BV and vaginitis were found to have a statistically significant association with preterm delivery. Effective diagnosis of vaginal infections/abnormal vaginal microbiota associated with preterm delivery can be achieved by the adjunct of microbiological smear examination of the vaginal smears to the clinical examination in limited resource settings.
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Introduction

Vaginitis among women of child bearing age is well acknowledged as a public health concern due to its high occurrence. Based on the microbial etiology, infectious vaginitis is classified broadly as Bacterial vaginosis (BV), Vulvovaginal Candidiasis (VVC) and Trichomoniasis. Role of these infections in the causation of preterm delivery and other adverse pregnancy outcomes has been well explored in the past few decades. More recently, vaginal dysbiosis (abnormal vaginal microbiota) during early stages of pregnancy is gaining recognition due to its positive association with adverse pregnancy outcomes [1,2]. Further, application of culture independent techniques such as phase contrast microscopy, broad range PCR and microbiome analysis of vaginal secretions has widened our knowledge regarding the microbial etiology of polymicrobial infections like BV and variations in the vaginal ecosystem among women from various ethnicities [3,4]. While, laboratory based diagnosis and confirmation of vaginal infections and/or abnormal vaginal microbiota is a part of routine antenatal care practices in developed nations, diagnosis and treatment of vaginal infections among pregnant women is solely based on clinical signs and symptomology of the patients in developing nations like India. With this background, we undertook the present study to estimate the proportion of vaginal infections/abnormal vaginal microbiota among south Indian pregnant women using clinical and microbiological investigations and find their association with preterm delivery.

Methodology

A case-cohort study was undertaken between May 2011 and April 2014 at an antenatal clinic of a secondary care hospital in South India. The study protocol was approved by the institutional ethical committee. Pregnant women in the age group of 18—35 years and 8—24 weeks of gestation were recruited in the study after obtaining a written informed consent. Women with history of medical diseases such as diabetes mellitus, hypertension, thyroid abnormalities, HIV and obstetric complications such as placental previa, cervical insufficiency and twin pregnancy were excluded from study.

Each study participant underwent a vaginal speculum examination and presence of inflammatory signs and/or vaginal discharge suggestive of infections were recorded. High-vaginal swabs were collected from the posterior fornix region for microbiological examination of vaginal infections. Vaginal pH testing, Whiff test and wet mount examination of the vaginal secretions for the presence of clue cells and motile trophozoites of *Trichomonas vaginalis* were performed at the patient bed side. Presence of three or more of the four Amsel criteria was diagnostic for Bacterial vaginosis [5]. One swab was transported to the microbiological laboratory using Stuart's transport media for aerobic and anaerobic microbiological culture techniques. A smear prepared from the high-vaginal swab of each woman was used for Gram's stain examination using Nugent's scoring system as originally described by Nugent RP et al. [6].

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Microbiological diagnosis of vaginal infections/abnormal vaginal microbial flora

Women harboring Nugent's Grade III vaginal flora were diagnosed as those having ''full'' bacterial vaginosis. Further, women harboring Grade II vaginal flora or Schroder's Lactobacillary Grade IIb pattern were classified as those having ''partial'' BV or vaginitis due to mixed bacterial etiology using the criteria reported previously [1,7]. Presence of Gram positive oval budding yeast cells with or without pseudohyphae along with more than five pus cells/OIF and microbiological culture positivity for *Candida* spp., was diagnostic for VVC. Presence of motile trophozoites of *T. vaginalis* on wet mount preparations of high-vaginal secretions was diagnostic for Trichomoniasis. Each high-vaginal swab was cultured using a Sabouraud's Dextrose agar plate for *Candida* spp., bilayered human blood agar with tween 80 for *G. vaginalis*, and sheep blood agar plate with and without a metronidazole disk (5 μg) in anaerobic and aerobic conditions respectively and a Colistin-Nalidixic acid blood agar plate for the isolation of Group B Streptococci. Identification of the aerobic culture isolates was performed using standard biochemical tests and anaerobes by Vitek 2 compact system (bioMérieux, Marcy-l'Etoile, France).

Obstetric outcomes of the study participants were recorded as mean period of gestation at delivery, late pregnancy loss (20—24 weeks of gestation) and preterm delivery (<37 weeks of gestation).

Statistical analysis

Data was analyzed using SPSS (ver 15.0. IBM, South East Asia, India). Descriptive statistics were used to estimate the proportion of individual infections among the study population. Microbiological diagnosis of infections was considered as the reference method to estimate the sensitivity, specificity, positive and negative predictive values of clinical diagnosis using 2×2 tables. Association of infections diagnosed using each criteria with preterm delivery was estimated using Fisher's exact *t*-test and statistical significance was considered when *p*-value was less than 0.05. Univariate analysis was used to estimate the Incidence risk ratio (with 95% CI) for preterm delivery among women with lower genital tract infections.

Results

A total of 790 women agreed to participate with an initial response rate of 95% in the present study. Mean age of the study population was 27.18 ± 3.54 years. Majority of the study participants were primi gravida (461, 58.3%), followed by second gravida (261, 33%) and third gravid women (68, 8.6%). Eight (1%) of the women recruited, reported a history of previous preterm delivery. The mean period of gestation during recruitment in the study and microbiological examination for infections was 14 ± 4.2 weeks. Data regarding the infection status of all 790 women was included for the analysis of the accuracies of clinical diagnosis in comparison with microbiological diagnosis. However, obstetric outcomes of 710 women were available for estimating the association of individual infections with preterm delivery, after excluding 16(2%) women with late pregnancy loss and 64 (8%) women who were lost during follow up by the end of the study.

Vaginal discharge was observed among 523 (66.2%) of the women. Among the women with vaginal discharge, white-thin homogenous discharge (170, 21.5%), white-curdy discharge (133, 16.8%), yellowish frothy discharge (119, 15%) and purulent discharge (101, 12.7%) were the predominant forms observed. Clinical diagnosis of lower genital tract infections was made among 270 (34.1%) women,

Table 1 Comparison of clinical and microbiological diagnostic results (2×2 tables) for BV, VVC and Trichomoniasis.

(a) Bacterial vaginosis

		Clinical diagnosis ($N = 790$)	
		Positive *n* (%)	Negative *n* (%)
Microbiological diagnosis	Positive	16 (2)	32 (4)
	Negative	6 (0.7)	736 (93)

(b) Vulvovaginal candidiasis

		Clinical diagnosis ($N = 790$)	
		Positive *n* (%)	Negative *n* (%)
Microbiological diagnosis	Positive	44 (5.5)	52 (6.5)
	Negative	87 (11)	607 (76.8)

(c) Trichomoniasis

		Clinical diagnosis ($N = 790$)	
		Positive *n* (%)	Negative *n* (%)
Microbiological diagnosis	Positive	44 (5.5)	52 (6.5)
	Negative	73 (9.2)	621 (78.2)

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Table 2 Sensitivity, specificity, positive and negative predictive values of clinical diagnosis of BV, VVC and Trichomoniasis in comparison with microbiological diagnosis.

Infection type	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Bacterial vaginosis	33.3 (20.4–48.4)	99.1 (98.2–99.7)	72.7 (49.7–89.2)	95.8 (94.1–97.1)
Vulvovaginal candidiasis	45.8 (36.6–56.3)	87.4 (84.7–89.8)	33.5 (25.5–42.3)	92.1 (89.7–94.0)
Trichomoniasis	45.8 (35.6–56.3)	89.4 (86.9–91.6)	37.6 (28.8–47.0)	92.2 (89.9–94.1)

whereas microbiological diagnosis was made among 259 (32.3%) of the women.

Proportion of women diagnosed with BV, VVC, and Trichomoniasis using microbiological examination was 5.9% ($n = 48$), 12.1% ($n = 96$) and 11.9% ($n = 94$) respectively, as compared to clinical diagnosis in 2.7% ($n = 22$), 16.5% ($n = 131$) and 14.8% ($n = 117$) of the women respectively. Of the 48 women diagnosed with BV using microbiological smear examination of the Gram stained high-vaginal smears, full BV was observed among 21 (2.6%) and partial BV in 27 (3.2%) of the women. Of the 22 (2.7%) women diagnosed with BV using Amsel's method, Nugent's score suggestive of BV (Full BV) was observed among 16 (72.2%) women. Treatment for BV in the form of clindamycin vaginal pessaries was given to 15 (37%) of the women based on the clinician's discretion in the present study. Microbiological confirmation among the women diagnosed clinically as VVC and Trichomoniasis could be achieved among 44 (33.5%) and 44 (37.6%) women respectively. Comparison of clinical and microbiological diagnostic results for BV, VVC and Trichomoniasis are depicted below (Table 1). Microbiological diagnosis of vaginitis by smear examination alone was observed among 75 (9.4%) women. Sensitivity, Specificity, PPV and NPV of clinical diagnosis of BV, VVC and Trichomoniasis in comparison with microbiological diagnosis are enlisted below (Table 2).

Detection rates and distribution of various microbes using microbiological culture among the total study population among women diagnosed with BV using Amsel's method and NSS is tabulated in Table 3. Detection rates of *Prevotella* spp., (9.6%, $n = 76$), *Porphyromonas* spp., (8.7%, $n = 69$) and *Bacteroides* spp., (11.3%, $n = 90$) were observed in the present study population and presence of any one of these three bacteria predominately in the culture was considered as the presence of Anaerobic Gram negative bacilli for analysis purpose. Culture positivity of Anaerobic Gram positive bacilli, that could not be identified using conventional biochemical identification techniques were

Table 3 Detection rates of individual microbe by microbiological culture of the high-vaginal swabs and their association with BV.

Microbe isolated on culture	Overall detection rate $N = 790$ n (%) 95% CI	BV by Amsel's method $N = 22$ n (%) 95% CI	Nugent's scoring system			
			Grade I $N = 654$ n (%) 95% CI	Grade II $N = 115$ n (%) 95% CI	Grade III $N = 21$ n (%) 95% CI	p-Value*
Lactobacillus spp.	763 (97) 95.8–98.1	19 (86.3) 71.9–100	638 (97) 95.6–98.3	105 (92.9) 88.2–97.5	20 (95.2) 86.0–100	0.032
G. vaginalis	45 (5.6) 4–7.2	16 (72.7) 54.0–91.3	3 (0.5) 0.04–1.04	22 (20.4) 13–27.7	20 (95.2) 86.0–100	<0.001
Candida spp.	124 (15.6) 13–18.1	3 (13.6) 0.7–27.9	92 (14.1) 11.4–16.7	31 (27.2) 19.0–35.3	1 (4.8) 4.3–13.9	0.001
Group B Streptococci	8 (1) 0.3–1.6	0	3 (0.5) 0.04–1.0	5 (4.4) 0.6–8.1	0	0.006
Anaerobic Gram Negative bacteria	98 (12.4) 10.1–14.1	20 (91) 79.0–100	3 (0.5) 0.04–1.04	77 (67.5) 58.9–76.0	18 (85.7) 70.7–100	<0.001
Anaerobic Gram Positive bacilli	79 (10) 7.9–12.0	6 (27.3) 8.6–45.9	15 (2.3) 1.1–3.4	57 (51.4) 42.2–60.5	7 (3.3) 4.3–10.9	<0.001

* Determined using Fischer's exact t-test.

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observed among 79 (10%) of the women. Higher detection rate of Anaerobic GPB was observed among women with Nugent's Grade II flora (women with partial BV and vaginitis).

Among the 710 women with obstetric outcomes, preterm delivery was observed among 54 (7.6%) of the women. Among these 54 women, 49 (90.7%) women had late preterm delivery (34—37 weeks of gestation) and 5 (9.25%) women had very preterm delivery (31—33 weeks of gestation). Mean period of gestation at delivery of the study population was 38.3 ± 1.3 weeks. Association of individual infections diagnosed using clinical and microbiological methods with preterm delivery is tabulated below (Table 4). Other probable etiology (non-infectious) of preterm delivery such as gestational hypertension and oligohydroamnios were observed among 3 and 4.2% of the study population during their follow up visits.

Table 4 Association of individual infections with preterm delivery in the study population estimated using Fischer's exact *t*-test and univariate analysis.

Infection status	Total $N = 710$ *n* (%)	Incidence rate for preterm delivery ($N = 54$) *n* (%)	Incidence risk ratio (95% CI) p-value
BV (Clinical)			
Yes	21(3)	4 (19)	2.62 (1.04—6.59)
No	689 (97)	50 (7.3)	0.04
BV (microbiological)			
a. Full BV			
Yes[a]	18 (2.5)	3 (16.7)	2.26 (0.77—6.56)
No	692 (97.5)	51 (7.4)	0.14
b. Partial BV			
Yes[a]	24 (3.4)	4 (16.7)	2.28 (0.89—5.81)
No	686 (96.6)	50 (7.3)	0.08
c. Full + Partial BV			
Yes[a]	42 (5.9)	7 (16.7)	2.4 (1.17—5.07)
No	668 (94.1)	47 (7.0)	0.018
VVC (clinical)			
Yes	115 (16.2)	11 (9.6)	1.32 (0.70—2.48)
No	595 (83.2)	43 (7.2)	0.38
VVC (microbiological)			
Yes[a]	84 (11.8)	7 (8.3)	1.1 (0.51—2.37)
No	626 (88.2)	47 (7.5)	0.78
Trichomoniasis (clinical)			
Yes	104 (14.6)	10 (9.6)	1.3 (0.68—2.54)
No	606 (85.4)	44 (7.3)	0.40
Trichomoniasis (microbiological)			
Yes[a]	84 (11.8)	5 (6.0)	0.76 (0.31—1.85)
No	626 (88.2)	49 (7.8)	0.54
Vaginitis (mixed bacterial etiology)			
Yes[a]	65 (9.2)	10 (15.4)	2.25 (1.19—4.26)
No	645 (90.8)	44 (6.8)	0.013

[a] Proportion of women diagnosed with each infection among the present study population.

Discussion

Vulvovaginal infection is one of the most common causes for a visit to a gynecologist among women of reproductively active age group. Elusive diagnosis based on clinical signs and symptomology alone is common which leads to persistence and/or recurrence of these infections [8]. However, need for accurate and early diagnosis of these infections is indispensable in view of the mounting evidence regarding the positive association of maternal genital tract infections during pregnancy with adverse pregnancy outcomes. In the present study, presence of vaginal discharge during per speculum examination suggestive of vaginal infections was observed among 523 pregnant women, among which, microbial etiology of vaginal infections could be recognized in 250 (47.8%) women. This finding re-emphasizes the previous reports indicating the possibility of detecting a microbial cause of vaginal infections/discharge in only 46—66% of the cases [9].

Positive predictive values for the clinical diagnosis of BV, VVC and Trichomoniasis were 72.7, 33.5 and 37.6% respectively in the present study. Among the four Amsel criteria, presence of clue cells showed high PPV of 100% while positive whiff test, vaginal pH >4.5 and homogenous discharge showed ppv of 41.6, 15.6 and 11% respectively. From these findings, the diagnostic supremacy of microscopic examination of the vaginal secretions for the presence of clue cells over the other three criteria for BV diagnosis is evident. We also observed positivity of more than 3 Amsel's criteria among three (4%) of 75 women diagnosed with vaginitis due to bacterial etiology. At least two Amsel's criteria were positive among 17 (22.6%) of the women with vaginitis. Using PCR based assays Srinivasan S et al. have reported the positivity of Amsel's criteria in the women when colonized with various bacteria in the absence of frank BV [10]. We assume the false positivity of the Amsel's individual criteria in women with vaginitis in the current study also might be due to the presence of bacteria like *Atopobium* spp and *M.hominis*, which could not be

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identified using smear microscopy. These findings emphasize the need for future studies to characterize the vaginal flora using molecular methods among women with positive Amsel's criteria. Also, findings regarding the utility of clinical diagnosis for VVC and Trichomoniasis from our study support the previous reports suggesting the low specificity or absence of clinical signs and symptoms in majority of the women with these infections [8,11].

Several restraining factors like high culture cost, time required for culture positivity and cumbersomeness of quantitative culture from polymicrobial specimens like high-vaginal swabs have grossly limited the utility of culture techniques for diagnosis of BV in our study. Despite the significant association of culture positivity of *G. vaginalis* with BV in the present study, presence of these bacteria also among women with normal and intermediate vaginal flora was also observed. This finding from our study and few other previously reported studies question the specificity of mere detection of *G. vaginalis* using culture for the diagnosis of BV [10,12]. Culture positivity rate of anaerobic Gram negative bacteria in our study was 85.7%, which is slightly higher than the rate of 30—70% reported among Indian pregnant women previously [13]. However, in view of the presence of few anaerobic Gram negative bacteria in small numbers as a part of normal vaginal flora as observed in our study and few other reviews reported previously [14,15], we re-emphasize the need of quantitative anaerobic culture techniques for diagnosis of BV. Similarly, *Candida* spp., was isolated using culture among 124 (15.6%) women, while its role as a pathogen could be demonstrated in 96 (12.1%) women. This finding supports the presence of Candida among 20—30% of pregnant women as a part of their endogenous normal vaginal flora, similar to the previous findings among non-pregnant women [16]. Despite microbiological culture for *T. vaginalis*, being the gold standard diagnostic method for Trichomoniasis [17,18], we used saline wet mount as the key diagnostic test for trichomoniasis in our study. Selection of smear microscopy over culture techniques for the diagnosis of trichomoniasis in the present study might be justified as the reports from low resource settings indicate comparable performance of both the techniques [19].

The present study observation regarding lack of association of full BV (diagnosed using stringent NSS) with preterm delivery is in agreement with few other studies reported previously [2]. Significant association of vaginitis due to mixed bacterial etiology with preterm delivery among our study population was observed. Also, we observed a significant association, when women having partial and full BVs were combined and tested for their association with preterm delivery. While findings regarding the presence and association of partial BV and vaginitis during pregnancy were prior reported from women of other ethnic groups [2,20,21], magnitude and the association of these two conditions with preterm delivery among Indian pregnant women is reported for the first time from the present study. With the overall low proportion of women with BV (48/790, 6%) and further loss of 6 women on follow ups, the present study had relatively a small cohort of 42 women with BV for the final outcome analysis. Of the 15 women who received specific antibiotic therapy for BV in the present study, three (20%) of them had preterm labor in comparison with 4/27 (14.8%) women, who did not receive treatment ($p = 0.66$). However, we advocate the need of evaluating the efficacy of treatment for BV in prevention of preterm delivery in the future employing larger sample size and better study designs. While we acknowledge the utility of NSS as an efficient diagnostic modality for epidemiological screening of BV in general population, we emphasize the indispensable need of examining the Gram's stained high-vaignal smears of pregnant women with abnormal vaginal flora for the presence of partial BV and vaginitis.

We recognize few limitations of our study. Microbiological screening for vaginal infections during later stages of pregnancy could not be repeated in the present study. If only this could be done, we could have estimated the proportion of women presenting with persistence or recurrence of infections and more importantly, the effect of treatment in curing these infections when diagnosed and treated solely based on clinical examination. Availability of a small sample size for comparing the diagnostic efficacy of Amsel criteria in comparison with NSS in the present study was also a limitation. Also, inability to employ quantitative microbiological cultures due to the high cost involved, restricted us to elucidate the exact microbial etiology of vaginitis and partial BV in our study population. Despite these limitations, our study findings could provide substantial evidence regarding the over/under diagnosis of vaginal infections, when solely done based on clinical examination.

Conclusion

Emphasis on the need for a two stepped diagnosis comprising of clinical diagnosis followed by microbiological laboratory based confirmation for vaginal infections was made by few researchers previously.

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However, diagnosis and prescription of antimicrobial therapy based on clinical examination alone is a common practice in developing nations like India. This is primarily attributable to the scant of diagnostic facilities and trained microbiologists to provide a laboratory based confirmation of the clinical diagnosis in low resource settings. Given this context, the present study findings underscore the utility of microbiological examination of the high-vaginal smears as an effective tool for assessing the lower genital tract health status among pregnant woman.

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Competing interest

None declared.

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