Correlation between bacterial vaginosis and adverse obstetric outcomes in Brazilian women

Correlação entre vaginose bacteriana e desfechos obstétricos desfavoráveis em mulheres brasileiras

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ABSTRACT

Introduction: Vaginal infections and modifications in the vaginal flora are very prevalent during pregnancy and have been associated with adverse obstetric outcomes, such as preterm labor, preterm premature rupture of membranes and low birth weight. **Objective:** To evaluate the prevalence and associations of bacterial vaginosis (BV) and pregnancy outcomes among Brazilian pregnant women in the third trimester. **Methods:** A prospective observational study was conducted assessing vaginal microbiota on bacterioscopy (wet mount and Gram stain), using vaginal swabs obtained from pregnant women between 26 and 32 weeks' gestation. The women were monitored until delivery, and their pregnancy outcome and demographic data were collected using an interviewer-administered questionnaire. **Results:** BV was assessed using both Amsel's criteria and Nugent's score in 77 of 190 women, resulting in the prevalence of 42.5%. BV was significantly associated with preterm labor (risk ratio [RR], 2.89; 95% confidence interval [CI], 2.35–3.56) and low birth weight (RR, 2.17; 95%CI, 1.61–2.92). Premature rupture of membranes was not associated with BV. **Conclusion:** BV was found to be very frequent among Brazilian pregnant women in the third trimester and correlated to unfortunate pregnancy outcomes. Regular screening of pregnant women may allow for early treatment and prevention of some obstetric complications.

Keywords: vaginosis, bacterial; pregnancy; pregnancy complications; premature birth; infant, low birth weight.

RESUMO

Introdução: Infecções vaginais e mudanças na flora vaginal são prevalentes durante a gravidez e têm sido associadas com desfechos obstétricos adversos, tais como trabalho de parto prematuro, amniorrexe prematura e baixo peso ao nascer. **Objetivos:** Correlacionar a presença de vaginose bacteriana (VB) com desfecho obstétrico desfavorável em mulheres brasileiras com gravidez no terceiro trimestre. **Métodos:** O estudo prospectivo observacional foi conduzido avaliando microbiota vaginal por bacterioscopia (a fresco e Gram) usando *swab* vaginal obtido de mulheres grávidas entre a 26 e a 32ª semanas de gestação. As mulheres foram monitoradas até o parto, e os dados de seu seguimento e os demográficos foram coletados por meio de um questionário autoaplicável. **Resultados:** Foi diagnosticada VB, com base nos critérios de Amsel e de Nugent, em 77 mulheres entre as 190, demonstrando prevalência de 42.5%. VB foi significativamente associada com maior risco de parto prematuro (*risk ratio* [RR], 2.89; 95% intervalo de confiança [IC], 2.35–3.56) e de baixo peso ao nascer (RR, 2.17; 95%IC, 1.61–2.92). A rotura prematura das membranas não foi associada com VB. **Conclusão:** Foi constatada alta frequência de VB entre as mulheres brasileiras grávidas no terceiro trimestre, e a BV correlacionou-se com piores prognósticos da gravidez. O rastreio rotineiro de mulheres grávidas pode permitir um tratamento precoce e a prevenção de algumas complicações obstétricas.

Palavras-chave: vaginose bacteriana; gravidez; complicações na gravidez; trabalho de parto prematuro; recém-nascido de baixo peso.

INTRODUCTION

Vaginal infections and modifications in the vaginal flora are very prevalent during pregnancy and have been associated with adverse obstetric outcomes, such as preterm labor (PTL), premature rupture of membranes (PROM) and low birth weights (LBW) [1,2]. Therefore, screening for vaginal infections during pregnancy could prevent perinatal complications, including preterm births[3].

A healthy vagina is populated by a myriad of commensal bacteria, which may, in exceptional situations, become pathogenic[3]. *Lactobacillus sp*. is the predominant bacterial species in the vaginal environment, which leads to an acidic pH (3.8 to 4.5), thus inhibiting the growth of potentially harmful agents[3-5]. The amount of *Lactobacillus sp.* morphotype when compared to other microorganisms found on a Gram stain of vaginal fluid determines the type of vaginal microbiota. When Gram staining shows *Lactobacillus sp.* composing 80% or more of the bacterial population, it is interpreted as flora type I. When there are approximately 50% *Lactobacillus sp.* and 50% other bacteria, it is interpreted as flora type II. When there are a clear predominance of other bacteria and a sharp decrease in the number of *Lactobacillus sp.* (<5%), it is interpreted as flora type III[3,6].

Under normal conditions, lactobacilli constitute 95% (flora type I) of the bacteria in the vagina and produce several antimicrobial compounds, including lactic acid and hydrogen peroxide (H_2O_2)[2]. Vaginas colonized with H_2O_2-producing lactobacilli remain persistently colonized with lactobacilli and are less likely to have bacterial vaginosis (BV)[3,4]. However, the absence or low concentration of *Lactobacillus sp.* (flora type III) is significantly associated with BV[2].

BV is a frequent clinical syndrome characterized by alterations in the normal vaginal flora leading to an accentuated decline or lack of the usual H_2O_2-producing lactobacilli and increase of anaerobic bacteria, such as *Gardnerella vaginalis*, *Mobiluncus*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Prevotella*, among other anaerobes[2].

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BV seems to be the most prevalent form of infection among pregnant women with PTL and PROM[3,7]. BV has been associated with an increased risk for PTL, especially in pregnancies under 32 weeks[1,7]. The anaerobic bacteria associated with BV release toxins which stimulate the decidua to produce cytokines such as inter-leucine-6 (IL-6) and tumor necrosis factor (TNF-α). These substances, in turn, provoke the production of prostaglandins involved in cervical collagen remodeling, thus increasing the risk of PTL[4].

Preterm birth is a major problem both in obstetrics and in neonatology, since it is one of the main causes of neonatal morbidity and mortality. The most common morbidities are Severe Acute Respiratory Syndrome (SARS), necrotizing enterocolitis, cerebral hemorrhage, as well as neurosensory disability (blindness, deafness), and delayed physical and mental development[1,6,7]. Preterm birth not only affects the child, but their families, and means more hospitalization and hospital costs[2,8,9].

Morbidity of genital infection in pregnant women is on the rise. Therefore, it is important to ensure etiological diagnosis[9,10]. Screening and proper treatment of genital infections in pregnant women, even when asymptomatic, are of vital importance since inadequate and inaccurate diagnosis generates misguided treatments[9,11].

OBJECTIVE

To evaluate the prevalence and associations of BV and pregnancy outcomes among Brazilian pregnant women in the third trimester.

METHODS

The study was conducted in a university maternity clinic, in the Northeast of Brazil, between May 2015 and January 2016. It was a prospective observational study conducted among healthy pregnant women who were registered at the prenatal clinic for the first time, *i.e.*, registration between 26 and 32 weeks' gestational age with or without symptoms.

To be included in the study, the pregnant woman needed to be apparently healthy and somewhere between the 26th and 32nd week of gestation. This period was chosen, since it is theoretically less prone to complications such as abortion and PTL[6,10,12].

Women were excluded of the study when under 18 years old, if they explicitly refused to participate, had a chronic degenerative disease, used immunosuppressive medication and/or antibiotics, used spermicides during sexual intercourse, had had vaginal intercourse or vaginally douched within the last 24 hours, or suffered from any type of vaginal bleeding.

Eligible women waiting for prenatal care were randomly selected and individually invited to participate. After discussing the objectives, responsibilities, and procedures, the volunteers who wished to participate signed the Informed Consent Form (ICF).

Pregnancy was confirmed by clinical data (minimum menstrual delay of eight days), β-HCG (>1.000 IU/L), or a transvaginal ultrasound showing the presence of a live embryo[6].

Vulvovaginitis diagnosis

Vulvovaginitis (VV) was diagnosed by using microscopy to analyze a suspension of vaginal fluid in 0.9% sodium chloride (NaCl) and smear Gram stained, after collecting material from the sidewall of the vagina. The vaginal content was put on glass slides, one for microscopic (wet mount) evaluation during the consultation and another one for Gram staining, performed in the Microbiology Laboratory, localized at Maternidade Escola Januário Cicco (MEJC), of the Universidade Federal do Rio Grande do Norte (UFRN), without prior knowledge of the case.

The pH was measured using colorimetric Merck® (Rio de Janeiro, Brazil) brand tape, which has a range of variations covering values from zero to 14. The tape was placed on the upper right third of the vaginal wall, avoiding contact with cervical mucus, and a reading was taken after one minute of contact.

The whiff test, consisted of placing vaginal fluid on a glass slide and adding two drops of 10% potassium hydroxide solution to see whether aromatic amines were released or not, was performed.

To prepare the wet mounts to identify the vaginal flora type, a sterile cotton swab was used to take samples from the upper right hand third of the vagina, and then placed in a glass bottle containing 1 mL of saline solution.

BV was diagnosed when at least three of the four Amsel criteria were met (homogeneous vaginal discharge, pH >4.5, clue cells >20%, positive whiff test) and a Nugent score of at least seven was obtained[13,14]. Vaginal trichomoniasis (VT) was diagnosed when the parasitic flagellate was found. The diagnostic of vulvovaginal candidiasis (VVC) was confirmed by the presence of hyphae or gram-positive blastospores.

Follow-up

Women diagnosed with BV, whether symptomatic or not, were treated with metronidazole vaginal cream for 10 days as soon as their results were obtained. All of the women were monitored until delivery. Pregnancy outcomes were recorded in a register for each patient, specifically for this study.

A means of identification was provided in the case notes, and the phone numbers of all the women were taken for ease of communication. All neonates in this study were observed for at least one week after delivery.

The following parameters were recorded for this study: gestational age at delivery (less or more than 37 weeks), rupture of amniotic membranes before arriving to the birthing place (yes or no), neonate birth weight (less or more 2,500 g) and Apgar score. The latter is widely used in maternity wards around the world to clinically evaluate neonatal health immediately after birth (values below 7 considered unfavorable).

Data collection and analysis

Data was collected using interviewer-administered questionnaires. The questionnaire, of which 202 were distributed, included questions on demographic characteristics and adverse pregnancy outcomes studied. PPROM was defined as rupture of membranes occurring at least one hour before the onset of labor pains. PTL was diagnosed as delivery occurring before 37 completed weeks of gestation. LBW was diagnosed as birth weight below 2,500 g at delivery.

The database was built using Stata 11 software (Stata Corp., Texas, Unites States). A univariate analysis of the sample was done, and the sample of women was described considering sociodemographic, clinical and behavioral aspects. Absolute and relative values of quantitative and categorical variables were described. The variables age, menarche, first sexual intercourse and number of children were dichotomized at the median. The correlation between VV, BV and sociodemographic, clinical and behavioral variables was measured using Fisher's exact test and the chi-square test (χ^2). Following this, relative risk (RR) and the respective confidence intervals were estimated for the bivariate analysis ($p<0.05$).

This study was approved by the Ethics Committee of the UFRN, Brazil, number 30951413.7.0000.5292.

RESULTS

Two hundred and twelve pregnant women were recruited for this study, but only 190 women were studied, since 22 were eliminated for lack of follow-up. Thirty-six of the women studied had BV, giving an overall prevalence of 19%. Of these, 58.3% had preterm delivery, 50% had LBW newborns and 63.8% had PPROM.

The age range of the study participants was 18 to 45 years old (mean age=27±4.5 years), 40.5% of these women had high school, most were mulattoes (46.8%), and 55.8% reported having a stable relationship. VV was diagnosed in 50.8% of women at the time of vaginal material collection, and 12.2% mentioned pathological vaginal discharge in the previous six months. Most patients reported less than three partners in the last year and at least one child (**Table 1**).

Table 2 shows that there was no statistical significance between the presence of BV and sociodemographic, clinical and behavioral variables of the studied patients, such as age, education, and ethnic group. Other variables studied were smoking, allergies, the number of children, menarche, first sexual intercourse, presence of sexually transmitted infections (STIs) in their partners and number of partners ($p>0.05$).

As shown in **Table 3**, BV was significantly associated with gestational age below 37 weeks ($p=0.001$; RR 2.897), and LBW ($p=0.001$; RR 2.175). PPROM and unfavorable Apgar scores were not associated with BV ($p>0.05$).

DISCUSSION

Vaginal discharge is a common situation in pregnancy, and often physiological. It can be explained, among other factors, by the hormonal changes and hypertrophy of the vaginal epithelium comprised of cells containing glycogen[4,6]. On the other hand, due to immunological factors inherent to pregnancy, pregnant women are more vulnerable to vaginal discharges of infectious character, which can harm both the mother and the fetus[3,6,10]. This pathogenicity has brought up the possibility of a strong correlation with cases of PTL, PPROM and LBW neonates. Recent studies have shown an increased need of preventive and therapeutic strategies to avoid these outcomes[8,9].

According to Farr et al.[15], pregnancy seems to be closely associated with VVC and VV, both related to possible obstetric complications, such as PTL. These results suggest that screening for vaginal colonization of *Candida* species, even in asymptomatic pregnant women, should occur regularly. When compared to women with normal flora, those with recurrent candidiasis had higher rates of PTL (11.9 *versus* 9.5%) and LBW neonates (10.8 *versus* 8%). Some researchers[12,15] suggest that asymptomatic *Candida* vaginal colonization could also be associated with PTL and LBW neonates. Thus, they justify routine screening and subsequent treatment to improve pregnancy outcomes. However, in our study, the presence of candidiasis in pregnant women did not increase the number of adverse obstetric outcomes.

In pregnant women, BV has been associated with PPROM, PTL and LBW neonates[1,2,10]. Accordingly, in our study the diagnosis of BV was significantly related to PTL and LBW newborns. The presence of VV was observed in 50.8% of our patients, while 40.5% had BV. In the BV group, PTL occurred in 100 women, and 78.3% had LBW neonates. We found a higher prevalence of BV and PTL than Svare et al.[1], that studied 3,262 Danish pregnant women and found BV in 16% of them and the rate of 5.2% of PTL. Afolabi et al.[2], studying Nigerian pregnant women, found a lower prevalence (26%) of BV when compared to our results, and BV was also significantly associated with PTL and LBW. It seems that, in addition to BV, socio-demographic variables, such as poor living conditions

Table 1 – Sociodemographic, behavioral and clinical characteristics of the pregnant women studied (n=190).

Categories	n	%
Age (≤27 years old)	96	50.5
Education		
Illiterate	3	1.6
Primary education incomplete	20	10.5
Primary education complete	76	40.0
High school	77	40.5
College incomplete	7	3.6
College complete	7	3.6
Marital status		
Single	31	15.7
Stable relationship	106	55.8
Separated/divorced	4	2.1
Widowed	1	0.5
Married	48	25.3
Ethnic group		
Caucasian	80	42.2
African-Brazilians	21	11.0
Mulattoes	89	46.8
Menarch age (≤12 years old)	93	50.3
First sex intercourse age (≤16 years old)	103	56.3
Vulvovaginitis (last 6 months)	24	12.2
Vulvovaginitis (current)	100	50.8
STI partners	5	2.6
Vaginal ejaculation *coitus* (per week)		
>4 *coitus*	57	32.2
3–4 *coitus*	120	67.8
Partners previous year		
≤2 partners	98	56.6
≥3 partners	75	43.4
Children (≤1)	137	72.1

STI: sexually transmitted infection.

Table 2 – Sociodemographic, behavioral and clinical characteristics related to bacterial vaginosis (BV) in pregnant women (n=190).

Variable	BV (+)		BV (-)		χ^2	RR	p-value	CI
	n	%	n	%				
Age (years old)								
≤27	39	40.6	57	59.4	0.000	1.005	1.000	0.712–1.418
≥28	38	40.4	56	59.6				
Education								
Up to high school	70	39.8	106	60.2	0.218	0.795	0.640	0.475–1.385
College	7	50.0	7	50.0				
Marital status								
Stable relationship	44	41.5	62	58.5	0.026	1.057	0.872	0.745–1.498
Others	33	39.3	51	60.7				
Ethnic group								
Caucasian	34	42.5	46	57.5	0.104	1.087	0.747	0.770–1.536
African-Brazilians/mulattoes	43	39.1	67	60.9				
Smoking								
Yes	4	44.4	5	55.6	0.000	1.102	1.000	0.520–2.337
No	73	40.3	108	59.7				
Other diseases								
Yes	18	33.3	36	66.7	1.229	0.768	0.268	0.503–1.173
No	59	43.4	77	56.6				
Allergies								
Yes	6	33.3	12	66.7	0.161	0.688	0.808	0.410–1.589
No	71	41.3	101	58.7				
Children								
≤1	52	38.0	85	62.0	0.991	0.805	0.320	0.563–1.149
≥2	25	47.2	28	52.8				
Menarch age (years old)								
≤12	35	37.6	58	62.4	0.260	0.888	0.610	0.623–1.265
≥13	39	42.4	53	57.6				
First sex intercourse age (years old)								
≤16	41	39.8	62	60.2	0.000	0.995	1.000	0.695–1.424
≥17	32	40.0	48	60.0				
STI partners								
Yes	1	20.0	4	80.0	0.236	0.487	0.627	0.084–2.834
No	76	41.1	109	58.9				
Vaginal ejaculation *coitus* (per week)								
>4 *coitus*	28	49.1	29	50.9	2.315	1.371	0.128	0.960–1.958
3–4 *coitus*	43	35.8	77	64.2				
Post anal sex ejaculation								
Yes	1	100.0	0	0.0	0.037	2.487	0.847	2.090–2.959
No	76	40.2	113	59.8				
Partners previous year								
≤2 partners	40	40.8	58	59.2	0.017	1.056	0.897	0.728–1.531
≥3 partners	29	38.7	46	61.3				

BV: Bacterial Vaginosis; χ^2: Chi-square test; RR: Relative Risk; CI: confidence interval; STI: sexually transmitted infection.

Table 3 – Relationship between bacterial vaginosis (BV) and adverse obstetric outcomes (n=190).

	BV (+)		BV (-)		χ^2	RR	p-value	CI
	n	%	n	%				
Apgar (1st minute)								
≤7	10	43.5	13	56.5	0.007	1.084	0.935	0.656–1.789
>7	67	40.1	100	59.9				
Gestacional age								
Preterm (<37 weeks)	21	100	0	0.0	27.570	2.897	0.001	2.352–3.567
Term (>37 weeks)	58	34.5	111	65.5				
Fetal weight (2,500 g)								
Below	18	78.3	8	21.7	13.196	2.175	0.001	1.617–2.927
Above	59	36.0	105	64.0				
Amniotic sac								
Disrupted	23	39.0	36	61.0	0.064	0.924	0.800	0.633–1.349
Intact	58	42.2	73	57.8				
Type of delivery								
Vaginal	36	40.9	54	59.1	0.000	0.988	1.000	0.701–1.393
Cesarean	41	41.4	58	58.6				

χ^2: Chi-square test; RR: relative risk; CI: confidence interval; Apgar score: a method to quickly summarize the health of neonate children.

and difficult access to health services, both inherent to underdeveloped countries, could also favor a greater prevalence of BV, as well as an increased risk of perinatal complications.

Several studies[18-20] have emphasized the importance of diagnosis and proper handling of genital diseases during pregnancy to prevent both maternal and fetal complications. These simple procedures can substantially impact health and reduce the costs of early hospital admission, thus improving management of financial resources. The introduction of routine laboratory screening tests during the prenatal care visits should be considered.

CONCLUSION

The evaluation of vaginal microbiota should be regularly assessed during pregnancy, even in asymptomatic patients, as part of routine examination[21]. In women with persistent discharge, screening for infections of the lower genital tract (vaginal and cervical) should be mandatory[8].

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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REFERENCES

1. Svare JA, Schmidt H, Hansen BB, Lose G. Bacterial vaginosis in a cohort of Danish pregnant women: prevalence and relationship with preterm delivery, low birthweight and perinatal infections. BJOG. 2006;113(12):1419-25.
2. Afolabi BB, Moses OE, Oduyebo OO. Bacterial Vaginosis and Pregnancy Outcome in Lagos, Nigeria. Open Forum Infect Dis. 2016;3(1):ofw030.
3. Tibaldi C, Cappello N, Latino MA, Polarolo G, Masuelli G, Cavallo F, et al. Maternal risk factors for abnormal vaginal flora during pregnancy. Int J Gynaecol Obstet. 2016 Apr;133(1):89-93.
4. Lamont RF, Sobel JD, Akins RA, Hassan SS, Chaiworapongsa T, Kusanovic JP, et al. The vaginal microbiome: new information about genital tract flora using molecular based techniques. BJOG. 2011 Apr;118(5):533-49.
5. Lindsay KL, Walsh CA, Brennan L, McAuliffe FM. Probiotics in pregnancy and maternal outcomes: a systematic review. J Matern Fetal Neonatal Med. 2013 May;26(8):772-8.
6. Zugaib M. Obstetricia básica. Barueri: Manole; 2015.
7. Denney JM, Culhane JF. Bacterial vaginosis: a problematic infection from both a perinatal and neonatal perspective. Semin Fetal Neonatal Med. 2009 Aug;14(4):200-3.
8. Sangkomkamhang US, Lumbiganon P, Prasertcharoensook W, Laopaiboon M. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery. Cochrane Database Syst Rev. 2015 Feb 1;(2):CD006178.
9. Koullali B, Oudijk MA, Nijman TA, Mol BW, Pajkrt E. Risk assessment and management to prevent preterm birth. Semin Fetal Neonatal Med. 2016 Apr;21(2):80-8.
10. Msuya SE, Uriyo J, Stray-Pedersen B, Sam NE, Mbizvo EM. The effectiveness of a syndromic approach in managing vaginal infections among pregnant women in northern Tanzania. East Afr J Public Health. 2009 Dec;6(3):263-7.
11. Modak T, Arora P, Agnes C, Ray R, Goswami S, Ghosh P, et al. Diagnosis of bacterial vaginosis in cases of abnormal vaginal discharge: comparison of clinical and microbiological criteria. J Infect Dev Ctries. 2011 May 28;5(5):353-60.
12. Nikolov A, Shopova E, Müseva A, Dimitrov A. Vaginal candida infection in the third trimester of pregnancy. Akush Ginekol (Sofiia). 2006;45(6):7-9.
13. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983 Jan;74(1):14-22.
14. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. 1991 Feb;29(2):297-301.
15. Farr A, Kiss H, Holzer I, Husslein P, Hagmann M, Petricevic L. Effect of asymptomatic vaginal colonization with *Candida albicans* on pregnancy outcome. Acta Obstet Gynecol Scand. 2015 Sep;94(9):989-96.
16. Mann JR, McDermott S, Zhou L, Barnes TL, Hardin J. Treatment of trichomoniasis in pregnancy and preterm birth: an observational study. J Womens Health (Larchmt). 2009 Apr;18(4):493-7.
17. van Schalkwyk J, Yudin MH, Infectious Disease Committee. Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis. J Obstet Gynaecol Can. 2015 Mar;37(3):266-74.
18. Lamont RF, Nhan-Chang CL, Sobel JD, Workowski K, Conde-Agudelo A, Romero R. Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011 Sep;205(3):177-90.
19. Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database Syst Rev. 2015 Jun 26;1:CD002250.
20. Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD000262.
21. Lamont RF. Advances in the Prevention of Infection-Related Preterm Birth. Front Immunol. 2015 Nov 16;6:566.
22. Roberts CL, Morris JM, Rickard KR, Giles WB, Simpson JM, Kotsiou G, et al. Protocol for a randomised controlled trial of treatment of asymptomatic candidiasis for the prevention of preterm birth. BMC Pregnancy Childbirth. 2011 Mar 11;11:19.

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