ORIGINAL RESEARCH ARTICLE

Vaginal *Candida* infection in pregnancy and its implications for fetal well-being

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Abstract

Vaginal *Candida* infection is one of the most common genital tract infections reported in pregnant women. This study was designed to determine the prevalence of vaginal *Candida* infection and pattern of *Candida* species isolates in the genital tract of pregnant women during antenatal period and in early labour; and the associated fetal outcome. The study was conducted at the antenatal clinic and labor ward of Olabisi Onabanjo University Teaching Hospital Sagamu, Ogun State, Nigeria. High vaginal swabs were collected from 408 pregnant women at the antenatal clinic and repeated in early labour. The samples were processed to isolate *Candida* species. Data were analysed using Statistical Package for Social Science (SPSS) windows version 21.0 (IBM Corp., Armonk, NY, USA). Prevalence of *Candida* infection was significantly higher in early labour (46%) than during antenatal period (38%) (P=0.02). *Candida albicans* was the predominant isolate, followed by *Candida glabrata* and *Candida tropicalis*. *Candida* infection was associated with increased likelihood of low birth weight babies (AOR 2.8, CI: 1.1-6.8; P= 0.03). However there was no statistically significant effect of *Candida* infection on the likelihood of preterm delivery (AOR 1.4, CI: 0.7-2.6; P= 0.35). Routine screening and prompt treatment of women at risk of delivering low birth weight babies is advocated. *(Afr J Reprod Health 2020; 24[3]: 33-40).*

Keywords: *Candida*; Pregnancy; Preterm birth; Prevalence

Résumé

L'infection vaginale à Candida est l'une des infections des voies génitales les plus courantes signalées chez les femmes enceintes. Cette étude a été conçue pour déterminer la prévalence de l'infection vaginale à Candida et le profil des isolats d'espèces de Candida dans le tractus génital des femmes enceintes pendant la période prénatale et au début du travail; et l'issue fœtale associée. L'étude a été menée à la clinique prénatale et au service d'accouchement de l'hôpital universitaire Olabisi Onabanjo de Sagamu, dans l'État d'Ogun, au Nigéria. Des écouvillons vaginaux élevés ont été prélevés sur 408 femmes enceintes à la clinique prénatale et répétés au début du travail. Les échantillons ont été traités pour isoler les espèces de Candida. Les données ont été analysées à l'aide de la version 21.0 de Windows Package for Social Science (SPSS) (IBM Corp., Armonk, NY, USA). La prévalence de l'infection à Candida était significativement plus élevée au début du travail (46%) qu'au cours de la période prénatale (38%) (P = 0,02). Candida albicans était l'isolat prédominant, suivi de Candida glabrata et Candida tropicalis. L'infection à Candida était associée à une probabilité accrue de bébés de faible poids à la naissance (AOR 2,8, IC: 1,1-6,8; P = 0,03). Cependant, il n'y avait aucun effet statistiquement significatif de l'infection à Candida sur la probabilité d'accouchement prématuré (AOR 1,4, IC: 0,7-2,6; P = 0,35). Le dépistage systématique et le traitement rapide des femmes à risque d'accoucher de bébés de faible poids à la naissance sont recommandés. *(Afr J Reprod Health 2020; 24[3]: 33-40).*

Mots-clés: *Candidose*; Grossesse; Naissance prématurée; Prévalence

Introduction

The human vagina usually has a predominance of *Lactobacillus* which helps to prevent colonization of the vagina by other potentially harmful microorganisms[1]. In pregnancy, the alterations in oestrogen and progesterone result in changes in vaginal acidity leading to overgrowth of anaerobic

bacteria and other harmful microorganisms in the vagina[2]. Vaginal douching, vaginal infections and treatment with broad spectrum antibiotics may also be associated with alterations in vagina flora[1,3]. Vaginal candidiasis is one of the most common genital tract infections reported in pregnant women[4,5]. The infection occurs more frequently in pregnant women compared to non-pregnant women[6]; a consequence of the high circulating estrogen in pregnancy which facilitates the adherence of *Candida* to the vagina mucosa. This is responsible for the more severe symptoms and persistent infections that are typical of vaginal candidiasis in pregnancy[7]. *Candida albicans* is the most common specie of *Candida* associated with vaginal candidiasis in pregnancy, however, other species such as *Candida glabrata, Candida tropicalis, Candida krusei, Candida parapsilosis, Candida pseudotropicalis and Candida stellatoidea* are increasingly becoming important[8,9]. Studies have shown that these non-albicans *Candida* species are often resistant to the commonly used anti-fungal drugs thus leading to persistent infection[10]. These non-albicans *Candida* species also typically require prolonged therapy before resolution of symptoms is achieved[7].

Some authors have reported that recurrent asymptomatic vaginal colonization with *Candida* species in early pregnancy is associated with preterm births and low birth weight babies[11]. There is also a suggestion that vaginal candidiasis may rarely cause ascending infection leading to *Candida* chorioamnionitis which has been associated with preterm labour, preterm prelabour rupture of membrane and cervical incompetence[12]. Studies have also shown that treatment of pregnant women with antifungal medications in pregnancy is associated with reduction in the incidence of preterm births[13]. This may justify screening for and treatment of *Candida* infection during pregnancy.

Although studies[4,5] in Nigeria have identified *Candida* to be quite common in pregnancy, only few of such studies described the different *Candida* species or reported fetal outcome. To the best of our knowledge, there are no studies in our environment on the pattern of *Candida* infection specifically in early labour. The knowledge of local epidemiology and the pattern of infection in pregnancy are important for prevention and management strategies. The aim of this study is to determine the prevalence of vaginal *Candida* infection and pattern of *Candida* species isolates in the genital tract of pregnant women during antenatal period and in early labour; and the associated fetal outcome.

Methods

This was a prospective longitudinal study conducted at the antenatal clinic and labour ward of Olabisi Onabanjo University Teaching Hospital Sagamu, Ogun State, Nigeria. The target population included all pregnant women with gestational age from 26 weeks to 32 weeks attending antenatal clinic at the hospital. The minimum sample size for the study was determined using the formula: ($n = Z^2pq/d^2$), where n is the desired sample size; Z is the normal standard deviation usually set at 1.96 which corresponds to the 95% confidence interval; p is the proportion in the target population; q =1-p and d is the degree of accuracy desired, set at 0.05. In a previous study[14] carried out among pregnant women in a tertiary hospital in Ogbomoso, Nigeria, the prevalence of vaginal candidiasis was 25%. The calculated sample size was 288. Addition of 10% of calculated sample size as allowance for attrition increased the sample size to 316. However, 408 eligible pregnant women were recruited consecutively from 1st of June 2017 to 31st of May 2019. Women with history of bleeding per vaginam or those who took antimicrobials within the preceding two weeks were excluded from the study. The pregnant women were given adequate information on the study and those who agreed to participate in the study signed a written consent form. The study participants were assured of the confidentiality of data obtained from them.

With the aid of a sterile disposable Cusco's speculum, vaginal secretion samples were taken from the posterior fornix using two sterile swab sticks. One swab was used for Gram's staining, and the other was inoculated on Sabouraud Dextrose Agar. The inoculated plates were incubated aerobically at 37^{o}C for 24 hours and subsequently for another 24 hours if there were no growths. Infection with *Candida* species was diagnosed by Gram-stained smear of specimen from the vagina

and colony growth on Sabouraud Dextrose Agar. Yeasts were identified in Gram stained smears as Gram-positive cells. Isolates were identified to specie level using CHROM agar Candida (Hardy Diagnostics, Santa Maria, CA). Susceptibility testing was performed on the banked isolates using disc dilution method according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines[15]. The antifungals and concentrations tested were fluconazole (0.12 to 128µg/ml) and nystatin (0.06 to 64µg/ml); the disc for clotrimazole was not available in the country. Those with positive *Candida* cultures received empirical therapy with Klovinal vaginal pessaries which contains metronidazole, clotrimazole and Lactobacillus spores. The Lactobacillus spores of Klovinal is to assist in maintaining normal vaginal ecosystem. Study participants were followed up until they presented in labour when a repeat sample collection was done prior to rupture of fetal membranes.

Information on the socio-demographic characteristics of the women, the gestational age at delivery and birth weight of babies was recorded in the data capture sheet. The socio-economic status of study participants was determined by allocating points for the education status of the women, and the occupation of the women and their partners. Women who attained up to primary, secondary and tertiary levels of education were scored 1, 2 and 3 points respectively. Women or partners with occupations corresponding to Civil Service grade levels 1-5 or those with low level/sustenance businesses were scored 1 point; those with occupation corresponding to Civil Service grade levels 6-10 or those with medium level businesses were scored 2 points while those with occupation corresponding to Civil Service grade levels 11-17 or those with high level businesses were scored 3 points. Women without supportive partners were allocated 0 point for partner's occupation. The aggregate scores were summed up and women with total scores of ≤ 3 points were classified as being of low socio-economic status, those with aggregate scores of 4-6 were classified as being of medium socio-economic status and those with aggregate scores of 7-9 were classified as being of high socio-economic status. The vaginal swab culture results at booking and in early labour were also recorded. The study was performed with the approval of the Health Research Ethics Committee of Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria (Reference number OOUTH/HREC/59/2016), in accordance with the declaration of Helsinki.

Statistical analysis

Data were analysed using Statistical Package for Social Science (SPSS) windows version 21.0 (IBM Corp., Armonk, NY, USA). The socio-demographic characteristics of the participants were presented using frequency table. Continuous variables were summarized using descriptive statistics such as mean and standard deviation at 95% confidence interval. A logistic regression model was used to ascertain the effects of *Candida* infection on the likelihood of preterm delivery and low birth weight babies after adjusting for potential confounders such as age, parity, educational level, socioeconomic status, birth weight and gestational age at delivery. The level of significance was set at *P*-value less than 0.05.

Results

A total of 408 pregnant women were recruited for the study at the antenatal clinic, however, 400(98.0%) had their deliveries at the study centre; the remaining 8 women were lost to follow up. Out of the 408 pregnant women sampled at the antenatal clinic, 155 were found to be positive for *Candida* species giving a prevalence of 38.0%; however, in early labour, 184 out of 400 pregnant women sampled were found to be positive for *Candida* species giving a prevalence of 46%. The prevalence of vagina *Candida* infection was significantly higher in early labour than during the antenatal period (OR= 1.39, CI= 1.05- 1.84, P= 0.02).

The socio-demographic characteristics of the study participants are presented in Table 1. Two hundred and two study participants (49.5%) were from the 20-29 year age group. The mean age was 29.4 ± 5.2 years while the range was 17-42 years. One hundred and sixty five study participants (40.4%) were nulliparous while 199(48.8%) had parity of 1-2. The median parity was 1. Majority of the women (60.3%) had tertiary

Table 1: Socio-demographic characteristics of study participants

Variable	Frequency	%
Maternal Age (years)		
≤ 19	7	1.7
20 – 29	202	49.5
30 – 39	190	46.6
≥ 40	9	2.2
Parity		
0	165	40.4
1-2	199	48.8
3- 4	42	10.3
≥ 5	2	0.5
Educational level		
≤ Primary	19	4.7
Secondary	143	35.0
Tertiary	246	60.3
Type of marriage		
Monogamy	382	93.6
Polygamy	26	6.4
Religion		
Christianity	308	75.5
Islam	98	24.0
Others	2	0.5
Socioeconomic status		
Low	77	18.9
Medium	317	77.7
High	14	3.4

Table 2: The distribution of *Candida* species isolates during antenatal period and early labour

***Candida* isolates**	**Colour on CHROM agar**	**Antenatal (N=155)**		**Labour (N=184)**	
		N	**%**	**n**	**%**
C. albicans	Green	93	60.0	138	75.0
C. glabrata	Purple	25	16.1	18	9.8
C. tropicalis	Metallic blue	12	7.7	10	5.4
C. krusei	Pink	2	1.3	12	6.5
Unidentifiable species*	White	6	3.9	4	2.2
Mixed growth	Mixed	17	11.0	2	1.1

*Species not identifiable on Chrome agar

education and 382 (93.6%) of the participants had monogamous marriage.

The distribution of *Candida* species isolates at antenatal clinic and early labour is depicted in Table 2. *Candida albicans* and *Candida glabrata* were the most prevalent species individually isolated in women at both antenatal clinic and early labour. Six *Candida* species (3.9%) could not be identified on Chrome agar in the antenatal clinic series while 4 *Candida* species (2.2%) could not be identified on Chrome agar in early labour series. Of all the women with positive *Candida* cultures, the proportion infected with *Candida albicans* species was significantly higher in early labour than during antenatal period (OR=2.0, CI=1.26-3.18, P=0.003).

Table 3 shows the sensitivity pattern of nystatin and fluconazole against the various *Candida* species. The overall sensitivity of nystatin was 58.8% while that of fluconazole was 65.6%. Seventy one percent of *Candida albicans* species were sensitive to fluconazole compared to 58.4% for nystatin. Out of the 14 *Candida krusei* isolates, none was sensitive to fluconazole while 9(64.3%) were sensitive to nystatin.

The overall mean gestational age at delivery (±SD) of the study participants was 38.5 ± 2.1 weeks. In *Candida* positive women, the mean gestational age at delivery (±SD) was 38.3 ±2.1 weeks; this was significantly lower than the mean gestational age at delivery of 38.7±2.2 weeks in *Candida n*egative women (P=0.046). The overall mean birth weight (±SD) of study participants was 3.1± 0.5 Kg. In *Candida* positive women, the mean birth weight (±SD) was 3.0 ±0.5 Kg; this was significantly lower than the mean birth weight of 3.2 ±0.5 Kg in *Candida* negative women (P=0.014).

In a logistic regression model with adjustment for potential confounders, *Candida* infection was associated with increased likelihood of low birth weight babies (AOR 2.8, CI: 1.1-6.8; P= 0.03) (Table 4). However there was no statistically significant effect of *Candida* infection on the likelihood of preterm delivery (AOR 1.4, CI: 0.7-2.6; P= 0.35) (Table 5).

Discussion

Vaginal *Candida* infection is usually discomforting to pregnant women and is often associated with the production of a thick, whitish, creamy or yellowish discharge[16]. The infection also raises some concern because of the perceived threat to the wellbeing of the baby[7]. This study has shown that vaginal candidiasis is common in pregnancy and prevalence is significantly higher in early labour than in the antenatal period. We also observed that vaginal *Candida* infection in labour was associated with a significantly increased likelihood of low birth babies but not preterm delivery.

Table 3: Antifungal sensitivity pattern (N =320)

Candida species	Total	Nystatin(%)	Fluconazole n(%)
C. albicans	231	135(58.4)	164(71.0)
C. glabrata	43	25(58.1)	27(62.8)
C. tropicalis	22	14(63.6)	13(59.1)
C. krusei	14	9(64.3)	0(0.0)
Unidentifiable species	10	5(50.0)	6(60.0)

*Mixed growth excluded

Table 4: Regression model to ascertain the effect of *Candida* infection on likelihood of low birth weight babies after adjusting for potential confounders

Predictor Variables		AOR	CI	P-value
Age	Per year	1.0	0.9-1.1	0.69
Parity	Per unit	1.3	0.9-1.9	0.13
Gestational age	Per week	0.6	0.5-0.7	<0.001*
Educational level	Primary	Reference		
	Secondary	0.3	0.1-1.5	0.14
	Tertiary	0.2	0.0-0.8	0.02*
Socioeconomic status	Low	Reference		
	Middle	1.7	0.5-5.4	0.38
	High	7.3	0.9-58.1	0.06
Culture result	*Candida* Negative	Reference		
	Candida positive	2.8	1.1-6.8	0.03*

*P<0.05 AOR- Adjusted Odds Ratio CI-Confidence Interval

Table 5: Regression model to ascertain the effect of *Candida* infection on likelihood of preterm delivery after adjusting for potential confounders

Predictor Variables		AOR	CI	P-value
Age	Per year	1.0	0.9-1.1	0.21
Parity	Per unit	1.1	0.8-1.4	0.65
Birth weight	Per unit Kg	0.1	0.1-0.2	<0.001*
Educational level	Primary	Reference		
	Secondary	3.9	0.4-34.8	0.22
	Tertiary	5.7	0.7-46.4	0.11
Socioeconomic status	Low	Reference		
	Middle	0.5	0.23-1.2	0.13
	High	0.6	0.1-3.6	0.55
Culture result	*Candida* Negative	Reference		
	Candida positive	1.4	0.7-2.6	0.35

*P<0.05 AOR- Adjusted Odds Ratio CI-Confidence Interval

The prevalence of genital *Candida* infection among women that presented in antenatal clinic was 38%. This is lower than findings from Maiduguri, North East Nigeria[17] where a prevalence of 41% was reported. The prevalence of vaginal candidiasis in pregnancy varies widely among different populations. In Ogbomosho, South West Nigeria, prevalence of 60% was reported while prevalence of 22.7% and 24.8% were reported in Burkina Faso and Argentina respectively[14,18,19]. Differences in hygienic, sexual and dietary practices are possible reasons for the wide disparity in prevalence of vagina candidiasis[14]. The prevalence of genital *Candida* infection among the women that presented in labour was 46% and this was significantly higher than prevalence in antenatal clinic. There are no studies in our environment on the prevalence of genital *Candida* infection in early labour. However, some authors[7,20] have reported that the highest prevalence of candidiasis occur in the third trimester. It has been postulated that conditions such as pH and temperature which

encourage colonization of *Candida*, are enhanced as gestational age advanced[8]. Another suggested mechanism is the immune down-regulation of the physiologic lower genital tract that occurs in late pregnancy[21]. The higher circulating estrogen, progesterone and corticosteroid levels in advanced gestation may also play a role by reducing the vaginal defense mechanism thereby enhancing the adherence of *Candida* to vagina mucosa thus leading to persistent infections[7]. The higher prevalence in labour may also indicate persistence of infections despite treatment in early pregnancy. This justifies the need for routine confirmation of successful treatments by repeat vaginal swab cultures after complete course of antifungals.

Candida albicans was the most predominant *Candida* species cultured in the study participants both at the antenatal clinic and in early labour. Similar findings have been previously reported[8]. This study also supports the view that *C.glabrata and C. tropicalis* are now becoming important causes of vaginitis[16]. This trend has been attributed to the arbitrary use of anti-fungal medications which eliminate the more sensitive *C.albicans* and selects resistant non-*albicans* species[22].

This study revealed that fluconazole was generally more effective against most *Candida* species than nystatin. This study also confirms the assertion that *Candida krusei* is universally resistant to fluconazole[23]. Unlike nystatin and clotrimazole, fluconazole is effective for treating vaginal candidiasis when administered orally; it is thus useful in situations when oral therapy is indicated such as the immediate postpartum period when lochial discharge may make vaginal therapy undesirable. Although some concerns have been expressed regarding the use of fluconazole during pregnancy especially during the first trimester, the consensus is that there is no increased risk of congenital malformations when administered orally as 150mg single dose[24,25]. There are no safety issues associated with use of nystatin and it is less expensive than fluconazole, however, there is a consensus from studies that nystatin is not as effective as the azoles[26]. Clotrimazole, another commonly prescribed azole has been found to be as equally effective as fluconazole[26], but is only useful for treating vaginal candidiasis when administered vaginally. The routine practice in our center now is to administer vaginal pessary containing a combination of metronidazole, clotrimazole and Lactobacillus spores (Klovinal) for vaginal candidiasis in pregnancy and oral fluconazole when treatment is indicated in immediate postpartum period.

There is some evidence to suggest that *Candida* vaginitis may be associated with adverse pregnancy outcomes[13,27]. In this study, women who had positive *Candida* cultures had a significantly lower mean birth weight and mean gestational age at delivery when compared with *Candida* negative women. Regression analysis also showed that women with vaginal *Candida* infection had increased likelihood of low birth weight babies. Although there was a higher odd of preterm delivery among women with vaginal *Candida* infection in labour, the trend was not statistically significant. Some other researchers have also reported that *Candida* colonization was not associated with preterm delivery[28]. It should be noted however that preterm and low birth weight babies have been found to have increased risk of *Candida* colonization and neonatal invasive candidiasis with associated increased morbidity and mortality[29]. This may justify screening and treatment of pregnant women with preterm labour to avoid these risks[28].

This study has a number of limitations. We did not consider the severity of colonization of *Candida* (mild, moderate or heavy); this may also affect the fetal outcomes. The presence or absence of bacterial isolates could also have some influence on fetal outcomes. Finally, the relatively small numbers of women with non-*albicans Candida* species calls for a larger comparative study that will better assess the effect of these species on fetal outcome.

Conclusion

This study has shown that vaginal *Candida* infection is common in pregnancy; and prevalence is significantly higher in early labour than in the antenatal period. *C.albicans* is the predominant species. *Candida* vaginitis increases the likelihood of low birth weight babies but not preterm delivery. However, considering the fact that both

preterm and low birth weight babies have increased risk of neonatal invasive candidiasis, there is need for a management protocol that ensures routine screening and prompt treatment of women in preterm labour or at risk of delivering low birth weight babies.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Contribution of Authors

AOSO conceived the study, AOSO and AAA designed the study, AAA, AAO, OAO, BAA, AKA, AIL managed the literature search and gathered data. AAA analysed the data, AAA wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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