Morbidities and mortality among infants of HIV-1-infected mothers with bacterial vaginosis in Kenya

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Keywords: neonatal mortality, neonatal morbidities, bacterial vaginosis, Kenya, HIV

Posted Date: June 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31175/v1

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Version of Record: A version of this preprint was published at Frontiers in Pediatrics on June 2nd, 2020. See the published version at https://doi.org/10.3389/fped.2021.544192.
Abstract

Background: This study aimed to assess the effects of maternal bacterial vaginosis (BV) on the morbidity and mortality of HIV-exposed infants of women enrolled in a randomized controlled trial (pre-dating antiretroviral therapy) at birth, 6 months, and 12 months.

Methods: Four hundred and twenty-five HIV-positive pregnant women were enrolled in this trial and were categorized as exposed if they had a laboratory-based diagnosis of BV (Nugent method). We compared the morbidity and mortality of infants of the mothers at birth, 6 months, and 12 months. We assessed morbidities from the mother’s history and clinical examination during scheduled and non-scheduled visits. The data that were collected longitudinally were then analyzed via multiple logistic regression with the generalized estimating equation. An independent correlation structure was assumed to evaluate the specific morbidity risks to infants associated with exposure to BV. We used the Kaplan–Meier method to generate the cumulative hazard curve, to determine mortalities at different stages between the two groups. Overall, only data for 328 infants were complete and used in the analysis.

Results: Data were available for 159 and 171 BV exposed and non-exposed mothers, respectively. Exposure to BV was not associated with any neonatal morbidity at birth, but was associated with adverse maternal condition (unadjusted odds ratio [OR], 2.93; 95% confidence interval [CI], 1.19–7.20, \( P=0.02 \)) and maternal hospital admissions (unadjusted OR, 1.95; 95% CI, 1.08–3.51, \( P=0.02 \)). At 6 months, infants of BV exposed mothers had higher odds of bloody stool (adjusted OR, 3.08; 95% CI, 1.11–10.00, \( P=0.04 \)), dehydration (adjusted OR, 2.94; 95% CI, 1.44–6.37, \( P=0.01 \)), vomiting (adjusted OR, 1.64; 95% CI, 1.06–2.56, \( P=0.03 \)), and mouth ulcers (adjusted OR, 12.8; 95% CI, 2.27–241.21, \( P=0.02 \)). At 12 months, exposure to BV was associated with dehydration (adjusted OR, 1.81; 95% CI, 1.05–3.19, \( P=0.03 \)) and vomiting (adjusted OR, 1.39; 95% CI, 1.01–1.92, \( P=0.04 \)). Kaplan–Meier survival analysis showed no association of BV with infant mortality (\( P=0.65 \)); however, the cumulative hazard curve showed a higher trend toward deaths among BV exposed infants.

Conclusion: Our findings demonstrate that BV is a good predictor of maternal and infant morbidities. Infants of both HIV and BV exposed mothers can manifest these symptoms at any stage within a year of growth. Adverse maternal condition and hospitalization of mothers after birth could indicate exposure to BV. Bloody stool, dehydration, vomiting, and mouth ulcers could indicate exposure to BV among infants.

1. Introduction

Bacterial vaginosis (BV), also referred to as vaginal dysbiosis, is a state characterized by altered vaginal biotas and a risk factor for birth complications, including low birth weight and preterm births. Current birthing practices are designed to optimize newborn exposure to maternal biota for which she already provides immunologic protection through transplacental immunoglobulin transfer and breastfeeding and thereby reduce the risk of infection (1), one of the leading causes of deaths among newborns.
A very high prevalence of BV has been described among human immunodeficiency virus (HIV)-infected women. However, data on the effects on child morbidity and mortality remain scarce in Kenya. A randomized trial of breastfeeding and formula feeding among antiretroviral drug naïve women provides an opportunity to determine whether BV increases the risk of early infant mortality and morbidity in this group of HIV-exposed infants.

Among immunosuppressed women who are HIV-infected, exposure to BV seems to be more indefatigable and common (2). BV characterized by a lack of *Lactobacillus bifidus* and predominance of anaerobic polybacteria (3, 4) such as *Streptococcus, Staphylococcus, Enterobacteriaceae, Candida albicans;* and *Trichomonas,* has well-known detrimental outcomes in exposed pregnant women. This includes spontaneous abortions and second-trimester miscarriages (5), fetal malpresentation, preterm birth (6, 7), postpartum infections, and rupture of membranes (8, 9). Increasing evidence suggests that low birth weight (LBW) and very low birth weight among infants were associated with BV (10), early neonatal deaths (11), as well as compromised immunity.

Although the incidence of BV varies from one country to the other and among different races, it is more frequent among women in sub-Saharan Africa and women of African ancestry in different parts of the world (7). For example, Alcendor (12) investigated health disparities in BV and its implications for HIV-1 acquisition in African-American women and reported prevalence rates of 52% and 32% among Black and Mexican American women respectively. Kamga et al. (13) reported a prevalence rate of 26% among pregnant women in Cameroon. In comparison, Nduati et al. (14) reported a prevalence rate of 47% in a cohort of HIV-positive pregnant women receiving care in Kenya. Other studies have reported a prevalence rate of 50% for BV among women who are HIV-positive (15). While the prevalences vary among studies, the negative consequences of the results analyzed have been detailed. However, the actual mechanisms underlying BV and the associated risk factors are still poorly understood (16). It is crucial to note that BV could afflict non-pregnant and pregnant women (13, 16) and can also occur in both sexually-active and -inactive young women (17), and in young and older women. Still, it is more pronounced among younger women (18).

Preliminary data comparing HIV-uninfected and -infected women showed very little differences in the vaginal biome of women. However, HIV-exposed sterile babies had different biomes from those of HIV-unexposed babies (19). This shows that there is an association between HIV and BV (2), making this a public health concern. Previous research showed that BV modifies the vaginal microbiome, and enhances the transmission of sexually transmitted diseases (STDs). A combination of an STD and BV is a potential disaster that requires timely detection, intervention, and eradication for proper growth and survival of the exposed infant. Several studies regarding coinfection of BV and HIV have been conducted. Some studies among HIV-infected women have revealed that BV is related to an increase in genital shedding of HIV RNA (20).

We hypothesized that BV was correlated with an increase in infections among infants and that it increases in the context of HIV. This study assessed several determinants of infant morbidity. We deduce
that the increase in morbidity is related to the development of abnormal microbiota among infants that exposes them to ailments. Simultaneously, maternal HIV infection has been linked to the negligible provision of resistant immunity against ordinary germs among infants (21). Since any strategy aimed at tackling diseases focuses more on risk factors, it is essential to understand any risk factors associated with BV. Interventions targeting these novel risk factors associated with BV could lead to more effective prevention of morbidities and mortalities affecting mothers and infants.

The risk factors associated with BV in the context of HIV are poorly understood as there have been no reports in these regards. Studies on BV in the context of HIV are few (22, 23, 24, 25). Still, limited results and data have emanated from Kenya regarding the prevalence and associated risk factors among HIV-exposed women. The few studies conducted were cross-sectional assay-based studies and only reported an increased risk of STDs among women exposed to BV and not necessarily the risk factors associated with this combination. Most available literature has focused on the health of infants during and after birth, ignoring that of the mother. The present study aimed to extend and investigate whether there are any differences in the health of mothers exposed to BV after birth. It has been argued that a healthy mother could positively impact the proper growth of her child. Several authors have cited the importance of a mother's care and Nduati et al. (14) reported higher mortality and morbidity rates among children whose mothers had died. Therefore, it is common knowledge that maternal health is an important determinant of infant health (16, 26). Since our work focuses on infant survival and wellbeing, it is inevitable to consider the aspect of maternal health as the two are interlinked. However, we would wish to refer readers to other papers published out of these data for more information regarding the relationship between maternal health and mortality (14, 27, 28). The potential effects of existing exposure to BV on mortality and morbidity remain poorly understood among women who have tested positive for HIV. Although a few studies have assessed the effect of birth-related complications on the maternal health status after birth, much attention has been accorded to these effects in first world countries. Our work focused on a resource-limited country (Kenya) whose HIV prevalence is still high. Understanding the differences in morbidity evolution at different times in the growth of infants, and birth-related complications in a country with limited resources would provide an excellent platform for better policy formulation, planning, and execution. The present study aimed to assess the impact of maternal BV on mortality and morbidity among HIV-exposed infants of women enrolled into a randomized clinical trial of breastfeeding and formula feeding (pre-dating anti-retroviral therapy) at birth, six months, and twelve months.

2. Methods

2.1 Study population, enrollment, delivery, and follow up

Sixteen thousand five hundred and twenty-nine women attending 4 antenatal clinics were screened for HIV from 6th November 1992 to 7th October 1997. Two thousand three hundred and fifteen (14%) were found to be HIV positive. One thousand seven hundred and eight were traced after they returned for results and a cohort of 425 was selected for the present study. The randomized women were
subjected to a standard interview and physical examination at each prenatal visit. At about 32 weeks of
pregnancy, pelvic examinations were performed, including the assessment of vaginal and cervical
secretions for HIV. In the present study, no woman was subjected to antiretroviral treatment. To determine
the viral load and CD4–8 cell counts, 15 ml of blood was collected. After delivery, blood was drawn from
each infant for testing, and the mother and infant pair was followed up every month in the first year. At
every visit, a history was obtained from the mother and the pair underwent physical examination.

2.2 Laboratory methods

The focus in this part was devoted to BV. Details on how other specimens were obtained have been
described elsewhere (14). Test specimens for BV and HIV-1 were collected via pelvic speculum
examination. This led to the collection of both vaginal and cervical specimens for HIV polymerase chain
reaction assays and screening for genital infection. The samples were collected using sterile Dacron
swabs and genital infections, including BV, were diagnosed and treated. Women were categorized as
having BV using the Nugent criterion (a pH of $\geq 7$ in the specimen was considered significant).

2.3 Clinical characteristics

The incidences of morbidities were both self-reported and recorded from hospital visits. Visits for the
assessment of clinical characteristics were either scheduled or non-scheduled. The occurrence of each
illness was recorded for every infant at each visit. Clinical assessment was performed during every
scheduled and non-scheduled visit, and morbidities were both self-reported and diagnosed at the clinic.
Clinical symptoms and signs were evaluated by the study coordinators via histories obtained regarding
infant and mother pairs, physical examinations of mother and infant pairs, and a standardized
questionnaire that had already been developed.

During birth and immediately after birth, several clinical characteristics were assessed for both neonates
and mothers. Among mothers, we considered signs that were indicative of complications, including
excessive bleeding, urinary tract infection, and hypertension. Among neonates, in-hospital characteristics
were classified as admissions lasting longer than 24 hours (classified as yes or no) and the number of
days spent at the hospital. Other characteristics of neonates were assessed by measuring the length (cm)
after birth, head circumference (cm), and weight (g). Apgar and Dubowitz scores were determined within
two hours after birth and assessed the physical characteristics of the baby and assigned ratings based
on the skin texture, reflexes, appearance, and motor functions. Healthier babies were assigned higher
scores (ranging from 0–10). Neonates who showed no signs of life were scored 0, while the healthiest
were scored 10. Maturity was assessed based on the gestational age at birth and any delivery that
occurred below 37 weeks of gestation was classified as premature. Any issues of breathing were
classified as respiratory distress. We also assessed the neonates for jaundice, conjunctivitis, and eczema.
We also assessed other clinical characteristics of infants at 6 and 12 months, including but not limited to
pneumonia, ear infection, lymphadenopathy, diarrhea, encephalopathy, sepsis, dehydration,
gastroenteritis, vomiting, wheezing, hematologic conditions, cold, otitis, fever, cough, malaria, thrush,
difficulty in feeding, rashes, scabies, oral ulcers, and any form of hospitalization (both admissions and non-admissions).

The study protocol was approved by the ethics review boards of the University of Washington and the University of Nairobi.

2.4 Statistical analysis

The effects of BV on neonates and mothers in the Nairobi study were described using adjusted and unadjusted odds ratios. Continuous variables were reported as means and standard deviations while categorical variables were reported as frequencies and proportions. Categorical items were assessed using Pearson’s chi-squared test. All variables were assessed and included in the multiple logistic regression model with adjustment for selected morbidity incidences at 6 and 12 months. This was performed under the generalized estimating equation framework. The inclusion of all the variables was supported by the fact that some variables which were not significant or associated with BV were significant in the multiple logistic regression in what is referred to as the suppressor effect (29, 30, 31). Finally, to assess the effects of BV on survival, we used the Kaplan–Meier method to identify any differences between the two groups. All statistical analyses were performed using R version 3.6.3 (R Development Core Team, Vienna, Austria). Analysis items with $P<0.05$ were considered statistically significant.

3. Results

At the time of delivery, after excluding stillbirths and second-born twins, 401 dyad pairs remained. At birth, which constituted the beginning of our analysis, data regarding 348 pairs were available for analysis. Forty-three cases were filtered due to missing data on the maternal status of BV. Of the remaining 348 cases, 20 were excluded from further analysis for the following reasons: 14 babies died and their morbidity measures were not assessed thereafter and 6 mothers were lost to follow up; however, the mother’s condition was examined and the analysis comprised these women. The 328 remaining pairs were included in the final analysis. Among them, 157 tested positive for BV (vaginal pH $\geq 7$), while the remaining 171 tested negative (vaginal pH $<7$).

Table 1A presents the selected maternal morbidity incidences in relation to BV exposure. There were significant differences between the two groups. Among the women with data on maternal conditions at delivery, compared to unexposed women, women diagnosed with BV had a higher prevalence of maternal complications (18/169 [10.6%] vs. 7/179 [4%]). Women with BV had a higher rate of hospital admission (35/135 [26%]) compared to women without BV (21/179 [15%]). The mean duration of hospital admission was 1.3±3.2 days among women with BV compared to 0.7±2.7 days among women with BV. Exposed mothers were 2.93 times likelier (95% CI, 1.24–7.71) to report adverse maternal conditions and 1.95 times likelier (95% CI, 1.08–3.51) to be admitted to the hospital at birth ($P=0.02$). Adjusting for the two variables did not yield statistical significance (Table 1B).
Table 2A shows the characteristics of neonates after birth. Neonates exposed to BV were comparable to unexposed babies in terms of gestational age, Apgar score, and anthropometric measures of weight and height. There were fewer male infants among babies exposed to BV compared to unexposed babies (81/179 [45%] vs. 99/178 [55%]). However, there were more deaths in the exposed group (9 [5%]) than in the unexposed group (5 [2.8%]). On average, BV unexposed infants had a higher mean body length (48.6±2.5 cm) than BV exposed infants (48.1±4.3 cm). Overall, 5 (3%) of 169 babies exposed to BV had an LBW (<2500 g) compared to 1 (1%) of 178 unexposed infants. The infants in the two groups had a similar distribution of neonatal morbidities since both the adjusted and unadjusted odds ratios did not yield any significant differences at the 0.05 level (Table 2B).

Table 3 presents the association between exposure to BV and birthweight which had been shown in other studies to be the most important independent predictor of BV, whereby a non-linear association was reported. Exposed neonates had 0.96 times odds of weight compared to unexposed neonates, but without statistical significance at the 0.05 level.

Table 4 presents the overall morbidity incidences ever reported among infants during the year. In the test of association between BV and the various morbidities, only hepatomegaly and cold showed statistical significance. No other morbidities assessed showed any association with BV ($P>0.05$).

Table 5 shows adjusted and unadjusted odds ratios for morbidity incidences at 6 and 12 months. At 6 months, infants of exposed mothers had higher odds of passing bloody stool, dehydration, vomiting, and mouth ulcers. At 12 months, the exposed group had higher odds of dehydration, hospital non-admissions, and vomiting. The other characteristics assessed were not significant at the 0.05 level.

Table 6 presents the relationship between BV and viral load. There was no significant difference between the two groups regarding viral load (odds ratio, 1.21; 95% CI, 0.91–1.60, $P=0.192$).

3.1 Mortality in the first twelve months of life

We compared survival between infants whose mothers were exposed and those whose mothers were not (Figure 1). There was no significant difference in the mortality distribution between the two groups ($P=0.65$); however, the graph showed a trend of higher mortalities in the BV exposed group. Though not directly associated with mortality, morbidity remained a major predictor of mortality. Therefore, we can conclude that a causal relationship exists between BV and mortality.

4. Discussion

The results of this study suggest that exposure to BV has a significant effect on the incidence of morbidity among babies and their mothers. We extensively analyzed the data at three preselected time points: at birth, 6 months, and 12 months. The reason for using these time points in our assessment of infants is the critical role they play in the optimal growth of the child, his/her development, and overall health.
As supported by the literature, in the assessment of neonates, no morbidity showed statistically significant results even after adjustment for other morbidities. This has previously been reported by Nduati et al. (14). However, our study showed adverse neonatal effects among the exposed subjects, similar to that reported by Dingens et al. in 2016 (18). Several studies have established an association between BV and various morbidities. For example, Hillier et al. (32) reported that exposed women had twice the chance of giving birth to children with LBW. Our analysis (which yielded nonsignificant results at the 0.05 alpha level) showed a 0.95 times likelihood of LBW among exposed subjects. The lower mean birth weight in the exposed group is also a good pointer to the consistencies in association as reported in other related studies (5,10,16).

Hospital visits (including admissions and non-admissions) for different morbidities have been investigated by several authors. Maternal hospitalization after birth has drawn the interest of researchers and particularly in developed countries, there has been a trend toward shortening the postpartum stay in hospital. Some of the factors include cost and availability of hospital beds for other mothers in need of care. Evans et al. (2018) investigated the impact of early discharge on outcomes among infants and found no differences in the outcomes of early and late discharge. However, the authors conducted a meta-analysis on the same data and found no study that reported any differences, even though there was an international trend toward shortening the postpartum length of stay in hospitals among women who have undergone vaginal delivery to improve the mother's sleep, for proper bonding of the mother and infant, and to protect the infant-mother dyad from nosocomial infections (33). Our analysis showed a 1.95-fold increase in the frequency of maternal hospital admissions among exposed subjects compared to non-exposed subjects. Although no benefit or risk has been associated with a longer stay in hospital, long admissions always have a cost implication. The hospitalization of infants has been investigated previously. Jones et al. (2018) investigated hospitalization as a result of general specific causes in Europe and reported higher odds among infants with jaundice and difficulty feeding. While our study does not specify the causes of hospitalization, it compares the odds of hospitalization between the two groups. From our results, there were no differences in hospitalization at 6 months; however, we reported higher odds among exposed subjects for both admissions and non-admissions. Although not statistically significant at the 0.05 alpha level, the results show a direction and strength of the effect, with a 1.12-fold increase among exposed and hospitalized subjects. Hospitalization is a very key indicator of health outcomes because in as much as an infant could be hospitalized due to specific morbidities, he/she may end up being diagnosed with a different morbidity which will also be treated. This could result in what we refer to as reverse causality, in which an unexposed subject could show higher odds for a disease than an exposed subject. This is evidenced by morbidity incidences regarding hepatomegaly, diarrhea, and difficulty feeding which showed higher odds among unexposed subjects at 12 months. Diarrhea, in contrast to our findings, has been found to be a good predictor of infant morbidity in other studies (34, 35, 36, 37). Lymphadenopathy and fever at 6 months, showed higher odds among unexposed subjects; as this result was incongruent to that reported in the literature, we performed further analyses. Infant hospitalization does not only have a negative effect on the development and physical growth of an infant, but also results in psychological distress and loss of parenting on the part of the mother (38). This
is one of the indicators of childhood morbidity as infants with longer periods of hospitalization tend to show higher morbidity rates due to the risk of disease exposure at care facilities, particularly in developing countries (39).

At 6 months, there was a 3.08-fold increase in the passage of bloody stool among exposed subjects, the results of which were significant at the 0.05 alpha level. A growing body of evidence has linked this with infant colitis and intestinal infections (40), which were not assessed as morbidities in the present study. Though not direct link with BV, our results suggest a causal relationship.

Another morbidity of interest is dehydration which yielded significant results at both 6 and 12 months. Finberg defined dehydration in infants as a loss of water and salt or extracellular fluid, caused by bacterial and viral agents (41). Our results showed a 2.94-fold and 1.181-fold increase in the rate of dehydration among exposed subjects at 6 and 12 months, respectively.

Vomiting has been associated with a 1.64-times and 1.39-times increase in odds among exposed subjects at 6 and 12 months, respectively, the results of which were significant at the 0.05 alpha level. Some authors have associated this with a lot of infant discomfort, thus hindering their optimal proper growth (42).

Finally, the other morbidity of interest is mouth ulcers. These, which vary in size, are open wounds that spread across the mouth lining of an infant and have diverse effects on their growth. Some direct effects include difficulty feeding as a result of pain, burning, and irritation of the mouth. A 12.8-fold increase at 6 months and a 2.34-fold increase at 12 months among exposed subjects demonstrates the seriousness of the effects of BV. This is a morbidity that requires proper intervention to enable proper growth of the infant.

The maternal viral load was investigated, and 1.21-fold odds were reported among exposed subjects, the results of which were not statistically significant. Our results were consistent with those reported by Burns et al. (43) who reported an association and a 3-fold odds of vaginal candidiasis among women infected with HIV but with low CD4 counts. In addition, a statistically significant association was reported by Atashili et al. (2008) between HIV and BV (23). Although there is no direct link between the CD4 count and viral load, low levels of the latter are desirable. Jamieson et al. (2001) reported on severe BV among women infected with HIV (2). The viral load is a very essential component, particularly in the context of HIV and an undetectable viral load is very desired as it reduces the risk of transmission, especially from mother to child. Mbori-Ngacha et al. (2001) reported that any BV could be treated during pregnancy (28); however, studies have shown that treatment does not scale down the adverse effects associated with preterm birth and neonatal risks (44, 45).

There has not been any published literature linking mortality directly to BV. However, there is an indirect link through the risk factors of BV. Preterm birth, pregnancy complications, and prematurity are risk factors that greatly affect neonates and infant mortality as reported in the Demographic and Health Surveys (46) and by other authors (47, 48). While, in their previous study, Nduati et al. excluded...
intrapartum deaths, stillbirths, and abortions (14), our analysis captured intrapartum deaths. Our Kaplan–Meier analysis through the cumulative hazard plot showed no differences in the hazard of mortality (p=0.65); however, the graph showed a trend toward a higher mortality rate in the BV exposed group. Therefore, this means that the risk of mortality still exists among infants whose mothers are exposed to BV.

In conclusion, our results were consistent with those reported in the literature and added further knowledge in the area of HIV. Our study showed that BV among HIV-exposed women could result in infants who are more vulnerable to several infections due to a compromised immune status. Assessing the risk of BV infection in HIV-positive women could be a step in the right direction of developing policies targeting limited resource countries that could finally mitigate the fatal adverse outcomes on mothers and their infants.

Declarations

Acknowledgement

We acknowledge Forgaty International Centre, National Institute of Health who funded the first Clinical Trial through grant registration number D43-TW00007 and T22-TW00001

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

Data is available from the second author upon reasonable request

Competing Interests

We declare there are no competing interests amongst ourselves

Ethical Statement

The initial study protocol was approved by the ethics review boards of the University of Washington and the University of Nairobi. We have reported that this was a secondary analysis of a randomized control trial. In the first analysis, the mothers were assigned to either breastfeeding or formula feeding. Full description of the study is attached as supporting file 1. The RCT was supported through Fogarty grant registration number D43-TW00007 and T22-TW00001. However, there was no RCT number provided at the time of conducting the study. In this paper, our focus was on secondary analysis of the data, in which we divided all the available data from the cohort of 425 into two. Women exposed to BV versus unexposed, and followed the babies from birth up to 1 year.
The first paper published with all additional details can be found here:

R. Nduati, G. John, D. Mbori-Ngacha, B. Richardson, J. Overbaugh, A. Mwatha, J. Ndinya-Achola, J. Bwayo, F. E. Onyango, J. Hughes, and J. Kreiss, “Effect of breastfeeding and formula feeding on transmission of hiv-1a randomized clinical trial,” JAMA, vol. 283, no. 9, pp. 1167–1174, Mar. 2000. [Online]. Available: https://doi.org/10.1001/jama.283.9.1167

Women agreeing to participate in the survey provided verbal consent.

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Tables

Table 1A. Outcomes of maternal morbidity incidence

| Maternal morbidity characteristics | Bacterial vaginosis exposed group | Bacterial vaginosis non-exposed group |
|-----------------------------------|----------------------------------|-------------------------------------|
| Adverse maternal conditions, % (n) | 10.6 (18/169)                   | 4 (7/179)                           |
| Maternal hospital admissions after birth, % (n) | 26 (35/135)                   | 15 (21/179)                         |
| Mean duration of admission, days | 1.3±3.2                      | 0.7±2.7                             |

Table 1B. Unadjusted and adjusted odds ratios

|                                | Unadjusted                  | Adjusted                  |
|--------------------------------|-----------------------------|---------------------------|
|                                | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| Adverse maternal conditions    | 2.93 (1.19–7.20)       | 0.02    | 2.25 (0.74–7.27)   | 0.16    |
| Maternal hospital admission after birth | 1.95 (1.08–3.51)       | 0.02    | 1.34 (0.63–2.88)   | 0.45    |

Data are reported as proportions (of patients with valid data) or mean ± standard deviation. P-values were derived from Fisher’s exact test.

Table 2A. Distribution of neonatal characteristics

| Neonatal characteristics | Bacterial vaginosis exposed group | Bacterial vaginosis unexposed group |
|--------------------------|----------------------------------|------------------------------------|
| Died, n (%)              | 9 (5.4)                          | 5 (2.8)                            |
| Birth weight per 100 g   | 31±5.5                           | 32±5.0                             |
| Length, cm               | 48.1±4.3                         | 48.6±2.45                          |
| Gender (male), n (%)     | 81 (46.5)                        | 99 (55.6)                          |
| Head circumference, cm   | 35.2±1.49                        | 35.2±1.59                          |
| Maturity, weeks of gestation | 39.5±2.35             | 39.8±2.03                          |
| Apgar score              | 9.63±1.29                        | 9.71±0.87                          |
| Maturity, Dubowitz score | 57.7±8.2                        | 57.8±8.11                          |
| Low birth weight (<2500 g), n (%) | 5 (3)                    | 1 (1)                              |

Table 2B. Unadjusted and adjusted odds ratios of morbidity incidence among the neonates
| Condition                  | Unadjusted                  | Adjusted                  |
|----------------------------|-----------------------------|---------------------------|
|                            | Odds ratio (95% CI)   | P-value                  | Odds ratio (95% CI)   | P-value                  |
| Jaundice                   | 1.2 (0.58–2.52)          | 0.62                     | 1.29 (0.58–2.92)      | 0.53                     |
| Conjunctivitis             | 1.39 (0.57–3.50)         | 0.47                     | 1.30 (0.52–3.33)      | 0.58                     |
| Lymphadenopathy            | 0.70 (0.30–1.57)         | 0.39                     | 0.67 (0.29–1.53)      | 0.35                     |
| Respiratory distress       | 1.03 (0.12–8.66)         | 0.98                     | 0.74 (0.03–10.63)     | 0.82                     |
| Skin rash                  | 0.93 (0.48–1.77)         | 0.82                     | 0.93 (0.48–1.80)      | 0.83                     |
| Prematurity                | 0.70 (0.09–4.29)         | 0.70                     | 0.21 (0.01–2.07)      | 0.25                     |
| Asphyxia                   | 1.06 (0.25–4.55)         | 0.93                     | 2.06 (0.30–20.30)     | 0.47                     |
| Pneumonia                  | 2.13 (0.20–46.12)        | 0.62                     | 2.79 (0.10–207.36)    | 0.58                     |
| Sepsis/meningitis          | 0.63 (0.13–2.60)         | 0.53                     | 0.56 (0.11–2.39)      | 0.44                     |
| Other abnormality on exam  | 1.29 (0.34–5.28)         | 0.71                     | 1.27 (0.33–5.32)      | 0.73                     |

Data are reported as proportions (of patients with valid data) or mean ± standard deviation. P-values were derived from Fisher's exact test.

**Table 3.** Odds ratio of bacterial vaginosis and birth weight as a continuous variable

| Condition                  | Odds ratio (95% CI) | P-value |
|----------------------------|---------------------|---------|
| Birth weight               | 0.96 (0.92–1.00)    | 0.08    |

**Table 4.** Overall morbidity incidences reported and correlation analysis of bacterial vaginosis and morbidity incidences
|                | Overall morbidity incidence, n (%) | Bacterial vaginosis status | Chi-squared test |
|----------------|-----------------------------------|---------------------------|-----------------|
|                |                                   | BV exposed, n (%)        | BV non-exposed, n (%) | P-value     |
| ia              | 111 (34)                          | 47 (30)                  | 64 (37)          | 0.2         |
| tion            | 32 (10)                           | 17 (10)                  | 15 (27)          | 0.5         |
| stool           | 38 (12)                           | 21 (13)                  | 17 (10)          | 0.3         |
| enopathy        | 140 (43)                          | 62 (39)                  | 78 (46)          | 0.3         |
| opathy          | 3 (1)                             | 1 (1)                    | 2 (1)            | 0.6         |
|                 |                                   | 22 (7)                   | 11 (7)           | 0.8         |
|owitz           | 78 (24)                           | 43 (27)                  | 35 (21)          | 0.1         |
| ion             | 5 (2)                             | 2 (2)                    | 3 (1)            | 0.7         |
| l               | 70 (21)                           | 30 (19)                  | 40 (23)          | 0.3         |
| egaly           | 47 (14)                           | 14 (9)                   | 33 (19)          | 0.007       |
|                 |                                   | 283 (86)                 | 129 (82)         | 0.04        |
|                 |                                   | 21 (6)                   | 9 (6)            | 0.6         |
| admitted        | 45 (14)                           | 20 (13)                  | 25 (15)          | 0.6         |
| non-admitted    | 169 (52)                          | 83 (53)                  | 86 (50)          | 0.6         |
|                 |                                   | 243 (74)                 | 111 (70)         | 0.2         |
|                 |                                   | 290 (88)                 | 134 (84)         | 0.1         |
|                 |                                   | 20 (6)                   | 7 (4)            | 0.2         |
|                 |                                   | 96 (29)                  | 43 (27)          | 0.5         |
|                 |                                   | 146 (45)                 | 72 (46)          | 0.6         |
| feeding         | 146 (45)                          | 72 (46)                  | 74 (43)          | 1.6         |
| l               | 120 (37)                          | 58 (37)                  | 62 (36)          | 0.9         |
| sh              | 64 (20)                           | 33 (21)                  | 31 (18)          | 0.5         |
| dermatitis      | 62 (19)                           | 28 (18)                  | 34 (20)          | 0.6         |
|                 |                                   | 63 (19)                  | 30 (19)          | 0.99        |
| :ers            | 15 (5)                            | 8 (5)                    | 7 (4)            | 0.7         |

Table 5. Adjusted and unadjusted odds ratios of morbidity incidences at 6 and 12 months
| Condition               | Six months Adjusted odds ratio (95% CI) |   | Twelve months Adjusted odds ratio (95% CI) |   |
|-------------------------|----------------------------------------|---|-------------------------------------------|---|
|                         |                                         |   |                                           |   |
| Pneumonia               | 1.14 (0.75–1.72)                       | 0.54 | 1.20 (0.88–1.65)                         | 0.25 |
| Ear infection           | 0.55 (0.18–1.54)                       | 0.27 | 0.63 (0.33–1.17)                         | 0.14 |
| Stool with blood        | 3.08 (1.11–10.00)                      | 0.04 | 1.19 (0.67–2.12)                         | 0.56 |
| Lymphadenopathy         | 0.74 (0.55–0.99)                       | 0.04 | 0.65 (0.52–0.82)                         | 0.01 |
| Encephalopathy          | 0.55 (0.07–3.57)                       | 0.53 | 0.51 (0.07–2.74)                         | 0.45 |
| Sepsis                  | 1.27 (0.55–2.96)                       | 0.57 | 1.18 (0.53–2.65)                         | 0.68 |
| Conjunctivitis          | 1.32 (0.84–2.08)                       | 0.24 | 1.41 (0.95–2.10)                         | 0.09 |
| Dehydration             | 2.94 (1.44–6.37)                       | 0.01 | 1.81 (1.05–3.19)                         | 0.03 |
| Wheezing                | 0.67 (0.34–1.27)                       | 0.22 | 0.87 (0.59–1.27)                         | 0.47 |
| Hepatomegaly            | 0.47 (0.19–1.05)                       | 0.08 | 0.56 (0.32–0.94)                         | 0.03 |
| Cold                    | 1.09 (0.88–1.35)                       | 0.44 | 0.99 (0.84–1.16)                         | 0.88 |
| Otitis                  | 1.10 (0.60–2.01)                       | 0.76 | 1.10 (0.79–1.55)                         | 0.57 |
| Hospital admitted       | 0.90 (0.46–1.73)                       | 0.75 | 1.01 (0.61–1.68)                         | 0.96 |
| Hospital non-admitted   | 0.99 (0.69–1.40)                       | 0.95 | 1.26 (1.01–1.61)                         | 0.07 |
| Fever                   | 0.75 (0.57–0.99)                       | 0.04 | 0.89 (0.73–1.07)                         | 0.22 |
| Cough                   | 0.97 (0.77–1.23)                       | 0.81 | 0.93 (0.78–1.10)                         | 0.39 |
| Diarrhea                | 0.72 (0.43–1.22)                       | 0.23 | 0.64 (0.45–0.89)                         | 0.01 |
| Thrush                  | 0.94 (0.64–1.37)                       | 0.74 | 0.92 (0.67–1.28)                         | 0.63 |
| Vomiting                | 1.64 (1.06–2.56)                       | 0.03 | 1.39 (1.01–1.92)                         | 0.04 |
| Difficulty feeding      | 0.74 (0.49–1.12)                       | 0.16 | 0.78 (0.63–0.97)                         | 0.02 |
| Heat rash               | 0.79 (0.55–1.13)                       | 0.2  | 0.75 (0.56–1.01)                         | 0.06 |
| Fungal rash             | 1.04 (0.62–1.77)                       | 0.87 | 1.15 (0.75–1.78)                         | 0.51 |
| Eczema/dermatitis       | 0.95 (0.76–1.19)                       | 0.67 | 0.87 (0.73–1.04)                         | 0.13 |
| Scabies                 | 0.78 (0.37–1.62)                       | 0.5  | 1.04 (0.69–1.55)                         | 0.86 |
| Mouth ulcers            | 12.8 (2.27–241.21)                     | 0.02 | 2.34 (1.00–6.03)                         | 0.06 |

*P*-values were derived from the chi-squared test

**Table 6.** Odds ratio of bacterial vaginosis and viral load

| Viral load | Odds ratio (95% CI) | P-value |
|------------|---------------------|---------|
|            | 1.21 (0.91–1.60)    | 0.19    |

**Figures**
Figure 1

Kaplan–Meier analysis of infant mortality over 12 months between infants with maternal exposure/ non-exposure to bacterial vaginosis