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Chlamydia trachomatis and *Neisseria gonorrhoeae* in HIV-infected Pregnant Women and Adverse Infant Outcomes

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Abstract

BACKGROUND—Sexually transmitted infections (STIs) in pregnancy such as *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) may lead to adverse infant outcomes.

METHODOLOGY—Individual urine specimens from HIV-infected pregnant women diagnosed with HIV during labor were collected at the time of infant birth and tested by polymerase chain reaction for CT and NG. Infant HIV infection was determined at 3 months with morbidity/mortality assessed through 6 months.

RESULTS—Of 1373 maternal urines, 277 (20.2%) were positive for CT and/or NG; 249 (18.1%) for CT, 63 (4.6%) for NG, and 35 (2.5%) for both CT and NG. HIV infection was diagnosed in 117 (8.5%) infants. Highest rates of adverse outcomes (sepsis, pneumonia, congenital syphilis, septic arthritis, conjunctivitis, low birth weight, preterm delivery, death) were noted in infants of women with CT and NG (23/35, 65.7%) compared to NG (16/28, 57.1%), CT (84/214, 39.3%), and no STI (405/1096, 37%, p=0.001). Death (11.4% vs. 3%, p=0.02), low birth weight (42.9% vs. 16.9%, p=0.001), and preterm delivery (28.6% vs. 10.2%, p=0.008) were higher among infants of CT and NG co-infected women. Infants who had any adverse outcome and were born to

women with CT and/or NG were 3.5 times more likely to be HIV-infected after controlling for maternal syphilis (OR 3.5, 95% CI 1.4-8.3). By adjusted multivariate logistic regression, infants born to mothers with any CT and/or NG were 1.35 times more likely to have an adverse outcome (OR 1.35, 95% CI 1.03-1.76).

CONCLUSION—STIs in HIV-infected pregnant women are associated with adverse outcomes in HIV-exposed infected and uninfected infants.

Keywords

HIV; pregnancy; chlamydia; gonorrhea; sexually transmitted infections; adverse infant outcomes

INTRODUCTION

In 2008, the World Health Organization estimated that 105.7 million new *Chlamydia trachomatis* (CT) and 106.1 million *Neisseria gonorrhoeae* (NG) infections occurred worldwide, with highest rates in low and middle-income countries.(1) Sexually transmitted infections (STIs) including CT and NG pose additional health risks for HIV-infected pregnant women. Untreated chlamydial and gonococcal infections in pregnancy can lead to fetal loss, premature rupture of membranes, and preterm labor and delivery.(2-6) Maternal chlamydial infections may lead to neonatal conjunctivitis and pneumonia, (4) whereas gonococcal infections may also predispose infants to conjunctivitis and in rare cases disseminated infections such as sepsis and septic arthritis.(3)

In response to limited published research from low and middle-income countries of HIV-infected pregnant women with CT and/or NG infections, the present sub-study aimed to assess the health of HIV-exposed infants in the first six months of life, particularly in association with these maternal STIs. We, therefore, evaluated adverse infant outcomes associated with these STIs during pregnancy including sepsis, pneumonia, congenital syphilis, septic arthritis, conjunctivitis, death, low birth weight, and premature delivery. In a separate report we described the prevalence of STIs in the NICHD HPTN 040 cohort and evaluated potential associations between maternal STIs and mother-to-child HIV transmission.(7)

METHODS

Study Design

This study was a sub-study of the National Institute of Child Health and Human Development (NICHD) HIV Prevention Trials Network (HPTN) 040 trial, also known as International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT P1043) NICHD/HPTN 040 (or P1043), a phase 3, triple-arm, randomized, open-label, multi-center study that evaluated the efficacy, safety, and tolerance of three different infant antiretroviral prophylaxis regimens for the prevention of intrapartum HIV transmission to infants born to HIV-infected pregnant women, who had not received antiretroviral drugs during pregnancy.(8) Study enrollment consisted of 1684 HIV-infected pregnant women diagnosed with HIV infection at the time of labor and delivery. All women provided written

informed consent. Enrollment occurred at multiple sites in Brazil, South Africa, Argentina, and the United States. Infants <32 weeks of gestational age were excluded from the study.

Maternal plasma HIV RNA levels and CD4+ T-lymphocyte subsets were obtained at the time of labor and delivery. Syphilis testing was performed at the time of labor and delivery using Venereal Disease Research Laboratory (VDRL) test titers with confirmatory treponemal syphilis antibody tests, per standard of care. The primary endpoint of the parent study was HIV infection status at 3 months of age. However, infants were followed until 6 months of age for safety and toxicity monitoring in the parent study. Adverse infant outcome data through age 6 months were collected, which included the variables of interest in this sub-study: sepsis, pneumonia, congenital syphilis, septic arthritis, conjunctivitis, death, low birth weight (<2500 g), and premature delivery (<37 weeks and ≥32 weeks).

HIV Diagnosis

HIV DNA polymerase chain reaction (PCR) was performed on infants within 48 hours of birth and at 10-14 days, 4-6 weeks, 3 months, and 6 months of age. Repeat HIV DNA PCR testing was performed to confirm a positive result. Diagnosis of infant HIV infection required two positive HIV DNA PCR test (Roche Molecular Systems Inc., Basel, Switzerland) results collected on different days. During the primary study, infants with a positive HIV DNA PCR test result at birth and positive results on repeat testing were classified as having *in utero* HIV infection. Infants with a negative HIV DNA PCR result at birth and a positive HIV DNA PCR result on subsequent testing were classified as having *intrapartum* HIV infection. All HIV-exposed infants enrolled in the study were exclusively formula fed.

Specimen Collection and Chlamydia and Gonorrhea Testing

Stored maternal urine samples, one per patient, collected at the time of labor and delivery or within 48 hours of birth were frozen at − 80 °C and stored at study sites. Stored urine was thawed and aliquots (7 mL each) were shipped on dry ice for testing at Cepheid, Sunnyvale, CA. Urines were tested for the presence of CT and NG using the Xpert® CT/NG assay. Results were reported as positive, negative or indeterminate. Indeterminate test results were repeated up to two times, and those that remained indeterminate were excluded from data analysis.

Statistical Analysis

Chi-square (or Fisher's exact) test was used to assess the difference in proportions of infants with adverse outcomes, including sepsis, pneumonia, congenital syphilis, septic arthritis, conjunctivitis, death, low birth weight (<2500g), and premature delivery (<37 weeks) according to maternal STI status (only CT-infected, only NG-infected, CT and NG co-infected, or CT and/or NG uninfected) and infant HIV status (HIV-infected (*in utero* and *intrapartum)* or HIV-uninfected), respectively. Univariate and multivariate logistic regression modeling (or exact logistic regression as necessary) was used to examine the relationship between adverse clinical outcome and infants born to women with CT and/or NG infection. All computations were done using SAS software v9.3 (Cary, NC, USA).

Human Subjects

Both the parent trial and the present analysis were approved by the institutional review boards and national ethics committees at each study site.

RESULTS

Urine samples from 1406 HIV-1 infected women were tested for CT and NG infections. After excluding 33 indeterminate results (2.3% of samples), 1373 maternal urine test results with linked infant outcomes (81.5% of the 1684 women enrolled in the original study) were included in the analysis. Women were from study sites in Brazil (68.3%), South Africa (29.8%), Argentina (1.4%), and the United States (0.5%). Further detail on the sociodemographics of our cohort was previously described in our earlier manuscript.(7) For the 1373 HIV-infected pregnant women included, 249 (18.1%) had any CT, 63 (4.6%) any NG, and 35 (2.5%) had both CT and NG; 277 women (20.2%) were positive overall for CT and/or NG. One hundred seventeen (8.5%) infants were HIV-infected including 75 (64.1%) infants infected *in utero* and 42 (35.9%) infants infected *intrapartum.* (Figure 1)

Adverse Infant Outcomes and Maternal Chlamydia and Gonorrhea

Of 1373 infants, 528 (38.5%) had at least one of the following adverse outcomes (sepsis, pneumonia, congenital syphilis, septic arthritis, conjunctivitis, death, low birth weight, or prematurity), and significant differences were noted among infants born to CT and/or NG infected as compared to uninfected women (p=0.001). The highest rates of any of those adverse outcomes were noted among infants born to women with both CT and NG (65.7%) as compared to those with NG only (57.1%), CT only (39.3%), and no STI (37%) (p=0.001). (Table 1)

In the cohort, 41 (3.0%) infant deaths occurred, and differences in infant death rates were noted among those born to STI-infected and uninfected women (p=0.02). Death rates were highest among infants born to women with CT and NG (11.4%) compared to those born to women with NG only (0%), CT only (1.9%), and CT or NG uninfected (3%) women.

Two hundred forty-four (17.8%) of the births resulted in low birth weight infants, whereas 148 (10.8%) infants were born preterm. Significant differences in birth weight (p=0.001) and preterm birth (p=0.008) were observed among infants born to women with and without these STIs. Low birth weight rates were highest among infants born to women with CT and NG (42.9%) compared to those born to women with NG only (21.4%), CT only (17.8%), and neither CT or NG (16.9%). Similar differences in death and low birth weight rates among these STI groups were noted when infants with congenital syphilis were excluded from the analysis.

Infants born to women with CT and NG had the highest rates of preterm delivery: 28.6% of infants born to women with CT and NG were born preterm in comparison to 10.2% of those born to women without CT or NG (p=0.008). Significant differences in infant adverse events were not noted among individual maternal STI groups (CT only, NG only, CT and NG, and no CT/NG) for infants with sepsis, pneumonia, congenital syphilis, or septic arthritis. The two cases of infant conjunctivitis occurred in women with CT.

Among 1373 infants, 117 (8.5%) were HIV-infected. Not surprisingly, differences in rates of any of the adverse events were noted when comparing HIV-infected (58.1%) versus HIV-uninfected infants (36.6%), (p<0.0001). Rates of sepsis (12% vs 3.3%, p<0.0001), pneumonia (18.8% vs 3.7%, p< 0.0001), congenital syphilis (10.3% vs 5.7%, p=0.05), death (13.7% vs 2%, p<0.0001), and low birth weight (25.6% vs 17%, p=0.02) were higher in HIV-infected versus HIV-uninfected infants. Infants who had adverse outcomes (Table 2) and were born to women with CT and/or NG were 3.5 times more likely to be HIV-infected (OR 3.5, 95% CI 1.4-8.3) after controlling for maternal syphilis infection. Similar adjusted associations were noted for individual adverse outcomes in infants exposed to maternal CT and/or NG and the likelihood of HIV infection: pneumonia (OR 4.7, 95% CI 1.5-14.9), and death (OR 6.3, 95% CI 1.4-28.1).

In an adjusted multivariate logistic regression controlling for infant HIV-infection status, the risk of any adverse infant outcome (e.g. including sepsis, pneumonia, low birth weight, prematurity and/or death) in infants born to mothers with CT, NG, or both was 1.35 (OR 1.35, 95% CI 1.03 – 1.76) times more than infants born to mothers without any STI. However, no associations were noted for individual infant adverse outcomes and those maternal STIs. (Table 3)

DISCUSSION

We evaluated the association of CT and NG infections with adverse infant outcomes. We found that infants born to HIV-infected women with CT and/or NG infection were more likely to have an adverse event through age 6 months as compared to infants born to HIV-infected women without these STIs. In our stratified analysis, the differences for death, low birth weight, and preterm delivery were most pronounced for those infants born to women with dual CT and NG infection.

Death in the first 6 months of life occurred in 11.4% of HIV-exposed infants born to women with CT and NG dual infection, but there was no mortality difference for those with only CT or only NG infections when compared to infants of mothers without either infection. Congenital syphilis and HIV-infection are known risk factors for infant death; however, these differences for CT and NG co-infection persisted even after controlling for these confounders.(9-11) Although limited, the few other existing published studies have also suggested that STIs such as CT or NG during pregnancy may be associated with increased rates of neonatal and infant death.(6, 12-15) One prior study found that stillbirth or neonatal death occurred 10 times more often among CT-infected women than uninfected matched controls.(13) Another study, which found reductions in neonatal death with presumptive STI treatment for *Trichomonas vaginalis*, bacterial vaginosis, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* in pregnancy, also provides some support for the causal association of maternal STIs in pregnancy and increased neonatal death.(16)

Preterm birth and low birth weight have been attributed to many different risk factors.(17, 18) It is likely that the women in our cohort had some degree of baseline risk for these types of outcomes, particularly given self-reports of high rates of prior preterm birth, usage of alcohol, tobacco, and illegal substances, and lack of prenatal care as discussed in our prior

analysis.(7) Nevertheless, our study provides additional support for the deleterious role of STIs and adverse birth outcomes such as preterm birth and low birth weight. These findings were particularly striking among the women infected with both CT and NG, where 42.9% delivered low birth weight infants and 28.6% had premature infants. These co-infected women also delivered infants with average birth weights that were 358.2g less than women uninfected with either of these STIs. Several studies apart from ours have previously suggested that STIs in pregnancy such as CT and/or NG may also be linked with delivery of low birth weight and/or premature infants. (6, 16, 19-24) However, studies that have focused on treatment of genital infections and/or chorioamnionitis have reported conflicting results with respect to improvement in birth outcomes with these interventions.(6, 16, 19, 24-29)

HIV infection during pregnancy, particularly in women with lower CD4 T-cell counts, higher serum HIV viral loads, and higher placental HIV viral loads, have also all been associated with an increased prevalence of low birth weight and/or premature infants.(30-33) Yet, our stratified analysis findings demonstrating that women with STIs had higher rates of low birth weight and premature infants remained, even after controlling for infant HIV status. Those findings were also not explained by high rates of untreated maternal syphilis (10%), as they persisted in a second analysis controlling for this variable. (34)

In fact, our findings may actually underestimate the extent of this problem since very low birth weight and early premature infants were unable to be included; gestational age ≥ 32 weeks was required for enrollment in the parent study.

In our evaluation of the effect of chlamydial and gonococcal infections during pregnancy and adverse events among a cohort of HIV-exposed infants, it may not be surprising that we found high overall rates of adverse outcomes and also significant differences in adverse outcome rates when comparing HIV-infected and HIV-uninfected infants. (31, 32, 35-37) (38-42) Existing research on HIV-exposed infants has suggested that HIV exposure alone may be a risk factor for other infections, particularly in infants born to women with advanced HIV infection, due to genital colonization of pathogens, subclinical chorioamnionitis, and lower protective antibody titers resulting in decreased transfer of passive immunity across the placenta.(43) However, while our infant cohort appeared to be at risk for adverse outcomes from HIV-exposure at baseline, we still found that infants born to CT and/or NG-infected mothers were more likely to have an adverse outcome, irrespective of infant HIV-infection. In our multivariate logistic regression analysis, although risk could not be associated with individual adverse outcomes (likely due to sample size), the risk of any adverse outcome was 1.36 times more likely in infants of women with CT and/or NG. When the analysis was adjusted for HIV-infection status, the risk of any adverse outcome remained essentially unchanged (adjusted odds ratio = 1.35).

One limitation of our study was that the sample size to evaluate the impact of STIs on infant outcomes in the first six months of life was based on convenience. The ability to detect differences in adverse infant outcomes by maternal STI group may have been limited by the modest sample size, particularly when STI exposures were combined with analysis of the infant HIV status. Furthermore, although data were collected on all types of serious adverse events and clinical outcomes that occurred in the parent study, our analysis was limited to

adverse infant outcomes that were more frequently reported with CT and/or NG infections as opposed to other nonspecific adverse outcomes such as respiratory distress, hypoglycemia, neutropenia, thrombocytopenia, gastroenteritis that were not included. These other types of adverse outcomes have been reported in a separate analysis of a cohort of 1000 HIV-exposed uninfected infants in NICHD HPTN 040.(44)

CONCLUSION

This study provides important information about the potential deleterious effects of untreated maternal STIs such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* on the well-being of infants born to high-risk groups of HIV-infected women in low and middle income countries. The combination of untreated CT and/or NG infection in pregnancy and HIV-exposure appears to increase the likelihood of adverse outcomes in these infants beyond the risk of HIV acquisition. This additional sub-study again highlights the potential benefits of prenatal laboratory-based STI screening and treatment programs, particularly for high risk groups such as HIV-infected pregnant women, which may aid in preventing these types of adverse infant outcomes.

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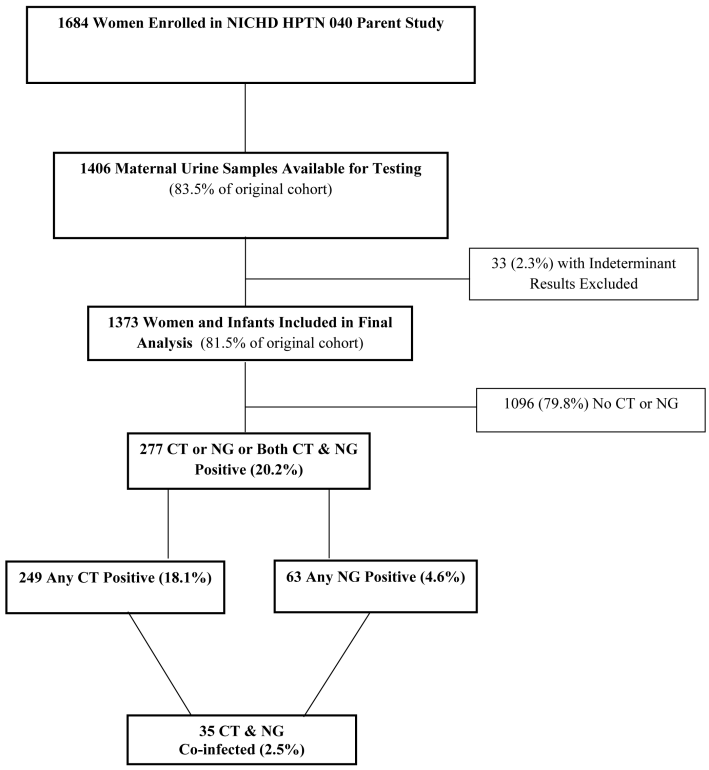

Figure 1.
Flow chart of subjects enrolled in the present analysis.

Table 1

Adverse Infant Outcomes by Sexually Transmitted Infection Status among Infants Born to HIV-infected Pregnant Women.

	Total (N = 1373)	CT & NG (N = 35)	CT Only (N = 214)	NG Only (N = 28)	No STI (N = 1096)	p value*
	n (%)	n (%)	n (%)	n (%)	n (%)	
Any of the following Adverse Infant Outcomes						
No	845 (61.5)	12 (34.3)	130 (60.8)	12 (42.9)	691 (63.0)	0.001
Yes	528 (38.5)	23 (65.7)	84 (39.3)	16 (57.1)	405 (37.0)	
Sepsis						
No	1318 (96.0	33 (94.3)	206 (96.3)	25 (89.3)	1054 (96.2)	0.30
Yes	55 (4.0)	2 (5.7)	8 (3.7)	3 (10.7)	42 (3.8)	
Pneumonia						
No	1305 (95.0)	33 (94.3)	204 (95.3)	24 (85.7)	1044 (95.3)	0.15
Yes	68 (5.0)	2 (5.7)	10 (4.7)	4 (14.3)	52 (4.7)	
Congenital Syphilis						
No	1289 (93.9)	32 (91.4)	203 (94.9)	26 (92.9)	1028 (93.8)	0.85
Yes	84 (6.1)	3 (8.6)	11 (5.1)	2 (7.1)	68 (6.2)	
Septic Arthritis						
No	1372 (99.9)	35 (100.0)	214 (100.0)	28 (100.0)	1095 (99.9)	0.97
Yes	1 (0.1)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.1)	
Conjunctivitis						
No	1371 (99.9)	35 (100.0)	212 (99.1)	28 (10 0.0)	1096 (100.0)	0.01
Yes	2 (0.1)	0 (0.00)	2 (0.9)	0 (0.00)	0 (0.00)	
Death						
No	1332 (97.0)	31 (88.6)	210 (98.1)	28 (100.0)	1063 (97.0)	0.02
Yes	41 (3.0)	4 (11.4)	4 (1.9)	0 (0.00)	33 (3.0)	
Low Birth Weight						
≥2500g	1129 (82.2)	20 (57.1)	176 (82.2)	22 (78.6)	911 (83.1)	0.001
<2500g	244 (17.8)	15 (42.9)	38 (17.8)	6 (21.4)	185 (16.9)	
Gestational Age						
≥ 37 weeks	1225 (89.2)	25 (71.4)	191 (89.2)	25 (89.3)	984 (89.8)	0.008
<37 weeks	148 (10.8)	10 (28.6)	23 (10.8)	3 (10.7)	112 (10.2)	

CT= *Chlamydia trachomatis*. NG= *Neisseria gonorrhoeae*.

*P-value calculated using Chi-square (or Fisher's exact) test between groups.

Table 2

Relationship of Infant HIV Infection Status with Adverse Infant Outcomes among Infants Born to HIV-infected Women with Any Sexually Transmitted Infection (CT/NG Including CT & NG Co-infection)

	Total (N=277) n (col %)	HIV-infected (N=28) n (row %)	HIV-uninfected (N=249) n (row %)	Unadjusted OR (95% CI)	Unadjusted p-value	Adjusted † OR (95% CI)	Adjusted † p-value
Any of the following Adverse Infant Outcomes							
No	154 (55.6)	8 (5.2)	146 (94.8)	1.00		1.00	
Yes	123 (44.4)	20 (16.3)	103 (83.7)	3.54 (1.50 - 8.36)	0.004	3.45 (1.43 - 8.31)	0.006
Sepsis							
No	264 (95.3)	26 (9.8)	238 (90.2)	1.00		1.00	
Yes	13 (4.7)	2 (15.4)	11 (84.6)	1.66 (0.35 - 7.92)	0.52	1.52 (0.31 - 7.40)	0.60
Pneumonia							
No	261 (94.2)	23 (8.8)	238 (91.2)	1.00		1.00	
Yes	16 (5.8)	5 (31.3)	11 (68.8)	4.70 (1.50 - 14.72)	0.008	4.74 (1.51 - 14.90)	0.008
Congenital Syphilis							
No	261 (94.2)	25 (9.6)	236 (90.4)	1.00		--	
Yes	16 (5.8)	3 (18.8)	13 (81.3)	2.18 (0.58 - 8.17)	0.25	--	
Septic Arthritis							
No	277 (100)	28 (10.1)	249 (89.9)	--		--	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	--		--	
Conjunctivitis							
No	275 (99.3)	28 (10.2)	247 (89.8)	1.00		1.00	
Yes	2 (0.7)	0 (0.0)	2 (100)	3.69 (0 – 31.24)	1.0	3.92 (0 – 33.21)	1.0
Death							
No	269 (97.1)	25 (9.3)	244 (90.7)	1.00		1.00	
Yes	8 (2.9)	3 (37.5)	5 (62.5)	5.86 (1.32 - 25.97)	0.02	6.30 (1.41 – 28.14)	0.016
Low Birth Weight							
≥ 2500g	218 (78.7)	22 (10.1)	196 (89.9)	1.00		1.00	
<2500g	59 (21.3)	6 (10.2)	53 (89.8)	1.01 (0.39 - 2.61)	0.99	0.95 (0.36 - 2.50)	0.92
Gestational Age							
≥ 37 weeks	241 (87.0)	22 (9.1)	219 (90.9)	1.00		1.00	
<37 weeks	36 (13.0)	6 (16.7)	30 (83.3)	1.99 (0.75 - 5.30)	0.17	2.08 (0.77 - 5.57)	0.15

CT= *Chlamydia trachomatis*. NG= *Neisseria gonorrhoeae*.

OR: odds ratio. CI: confidence interval. OR calculated by univariate or exact logistic regression as necessary.

[†]Each adverse infant outcome was adjusted for maternal syphilis status using multivariable logistic regression.

Table 3

Relationship of CT/NG with Adverse Infant Outcomes with/without Adjusting for Infant HIV Infection Status

	Unadjusted (Predictor = Any CT/NG)		After Adjusting for HIV status (Predictor – Any CT/NG + HIV Status)	
Adverse Infant Outcomes	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Any Adverse Infant Outcomes (yes)	1.36 (1.04 - 1.78)	0.02	1.35 (1.03 - 1.76)	0.03
Sepsis (yes)	1.24 (0.65 - 2.34)	0.51	1.19 (0.62 - 2.26)	0.60
Pneumonia (yes)	1.23 (0.69 - 2.19)	0.48	1.16 (0.65 - 2.10)	0.61
Low birth weight <2500g	1.33 (0.96 - 1.85)	0.086	1.32 (0.95 - 1.83)	0.099
Gestational age <37 weeks	1.31 (0.88 - 1.96)	0.18	1.31 (0.87 - 1.95)	0.19
Death (yes)	0.96 (0.44 - 2.10)	0.91	0.88 (0.40 - 1.96)	0.76

CT= *Chlamydia trachomatis*. NG= *Neisseria gonorrhoeae*. OR: odds ratio. CI: confidence interval.