Trans-Placental Transmission and Survival at Birth among Neonates of Chlamydia trachomatis Infected Mothers: A Cohort Study

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Abstract

Objective The study aimed at assessing trans-placental transmission of Chlamydia trachomatis (CT) and fetal survival at birth among CT infected mothers. Study Design This is a non-interventional prospective cohort study. Population /Study Setting The study was conducted among two thousand and fourteen pregnant women attending antenatal clinic at the Cape Coast Teaching Hospital. Methodology Cord blood from neonates born to one hundred and twelve (112) pregnant women whose cervical samples were positive for CT at first ANC visit were screened by Polymerase Chain Reaction (PCR) for CT infection. Transplacental transmission of CT was considered when CT DNA type-specific agreement was observed between the samples of maternal cervical specimen and the corresponding neonatal cord blood. A neonate who did not survive at birth at $>$ 28weeks gestation or 1000g birthweight is considered stillbirth. Results There were one hundred and one (101) live births and eleven (11) stillbirths. Of the 101 live births, two (2) of the cord bloods were CT DNA positive whereas nine (9) of the eleven (11) stillbirths were cord blood positive for CT DNA. The two (2) neonates with cord blood positive for CT DNA developed early onset neonatal sepsis. There is therefore, a strong evidence that trans-placental CT infection is associated with stillbirth P$<$ 0.001; OR, 38.5 ; 95% CI (6.91 – 412.3). Conclusion Antibiotic prophylaxis for pregnant women at risk for CT infection is recommended. Routine screening for all pregnant women should be considered for prenatal care in medium to long term planning.

Title Page

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Running Title

Funding

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Objective

The study aimed at assessing trans-placental transmission of*Chlamydia trachomatis* (CT) and fetal survival at birth among CT infected mothers.

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The study was conducted among two thousand and fourteen pregnant women attending antenatal clinic at the Cape Coast Teaching Hospital.

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Cord blood from neonates born to one hundred and twelve (112) pregnant women whose cervical samples were positive for CT at first ANC visit were screened by Polymerase Chain Reaction (PCR) for CT infection. Transplacental transmission of CT was considered when CT DNA type-specific agreement was observed between the samples of maternal cervical specimen and the corresponding neonatal cord blood. A neonate who did not survive at birth at $>$ 28weeks gestation or 1000g birthweight is considered stillbirth.

Results

There were one hundred and one (101) live births and eleven (11) stillbirths. Of the 101 live births, two (2) of the cord bloods were CT DNA positive whereas nine (9) of the eleven (11) stillbirths were cord blood positive for CT DNA. The two (2) neonates with cord blood positive for CT DNA developed early onset neonatal sepsis. There is therefore, a strong evidence that trans-placental CT infection is associated with stillbirth P$<$ 0.001; OR, 38.5 ; 95% CI (6.91 – 412.3).

Conclusion

Antibiotic prophylaxis for pregnant women at risk for CT infection is recommended. Routine screening for all pregnant women should be considered for prenatal care in medium to long term planning.

Tweetable Abstract

Transplacental transmission of *Chlamydia trachomatis* is associated with stillbirth in infected pregnant women where prenatal routine screening is unavailable .

Keywords

Trans-placental; Stillbirth; Chlamydia trachomatis; Neonates; survival at birth

Introduction

Screening and treatment of sexually transmitted infections (STIs) in pregnancy represents an overlooked opportunity to improve maternal and perinatal outcomes worldwide (1). Although *Chlamydia trachomatis (CT)* is the most commonly treatable bacterial STI, few countries have routine pregnancy screening and treatment programs for *CT*infections in pregnancy (2-4). CT infections in women usually would go undiagnosed since the infections are mostly asymptomatic and poses serious challenges to the management of the disease (4). The majority of infected individuals would report for care in the advanced stage or may report with complications since the infection remain asymptomatic for a long time (5-7)

CT infection has been implicated in several adverse obstetric outcomes; premature rapture of membrane, amnionitis, intrapartum fever, and meconium stained amniotic fluid (8, 9). These adverse pregnancy outcomes have been identified to be associated with neonatal sepsis (10). Similarly, adverse neonatal outcomes that were known to be associated with vertical transmission have also been reported by previous studies as preterm delivery, low birth weight and Apgar score less than 7 at minutes one and five (3, 10, 11). Spontaneous abortion and stillbirth have also been reported to be significantly associated with CT infection (11).

Vertical transmission of diseases occurs at one of these stages: in utero, intrapartum and postpartum. The severity of morbidity and mortality of most vertically transmitted diseases would depend on the gestational age at which the infection was acquired (12). Though vertical transmission of CT has been widely reported, there is paucity of literature on the gestational age at which the infections were transmitted to the fetus or the neonate. The impact of the various routes of transmission on the neonate is not well defined. The aim of the present study is to determine the relationship between trans-placental transmission of CT infection in pregnancy and survival at birth of the fetus.

Methodology

Study design:

This non-interventional prospective cohort study was conducted during the period of July 2010 and December 2016, among two thousand and fourteen (2014) pregnant women attending antenatal clinic at the Cape Coast Teaching Hospital, Central Region, Ghana.

Ethical Consideration

The Institutional Review Board of the University of Cape Coast approved the study. Permission was obtained from the hospital management before the commencement of the study. Participants also signed informed consent and were informed participation was voluntary and they could withdraw from the study anytime they choose to. They were also assured that neither participation nor non-participation would influence the care they received.

Sampling

Maternal Cervical sample

Maternal cervical samples were obtained from pregnant women on their first ANC visit, when they were recruited and their epidemiological data were obtained (10). The cervical samples were obtained using a cytopathological brush for sampling of the cervix. The samples were inoculated into TE solution (Tris HCl, pH 7.5 – 10 mM; EDTA, 1 mM), and stored at -20°C, until the deoxyribonucleic acid (DNA) for CT were extracted.

Neonatal Cord blood samples

Cord blood were obtained from neonates of the mothers who were positive for CT infection for assessment of trans-placental transmission having obtained informed consent from the mothers.

Cord blood were obtained from one hundred and twelve (112) neonates of CT DNA positive mothers at birth by observing the necessary precautions described by White et al (13). The samples were collected directly from one of the arteries of the cord using a 3 ml disposable syringe (27/5 needle) to obtain about 1 ml of fetal blood. The collection was performed after clamping the cord and complete delivery of the placenta and fetal membranes. The fetal blood was dispensed into a tube with EDTA and stored at - 20°C, until the CT DNA was extracted.

The PCR technique was applied for both maternal cervical specimens and neonatal cord blood as described by Schmidt et al (3).

Case definition

Transplacental transmission.

In this study, transplacental transmission of CT was considered when CT DNA type-specific agreement was observed between the samples of maternal cervical specimen and the corresponding neonatal cord blood.

Stillbirth

A neonate was classified as stillbirth based on the World Health Organization (WHO) definition. The WHO cutoff of 28 weeks or 1000 g for developing countries with the reason being that, in many low and middle-income countries, many neonates will not survive if born before 28 weeks' gestation.

Data analysis

Data was analyzed with SPSS 22. Fisher's exact test was used to compare stillbirth among cord blood positive and negative neonates at 95% confidence interval with $p < 0.05$ being significant.

Results and Discussion

One hundred and twelve (112) of the two thousand and fourteen (2014) mothers screened during the study period were positive for CT, a prevalence of 5.6%. The mean age of the respondents was 24+ 4.3years. The mean birth weight of the neonates was 2.98+ 2.2 kg. There were one hundred and one (101) live births and eleven (11) stillbirths. Two (2) out of the one hundred and one (101) live births had CT DNA positive cord blood, an indication of transplacental transmission of CT . Eleven (11) neonatal cord blood were positive for CT DNA. Out of the eleven neonates whose cord blood were CT DNA positive, nine (9) were stillborn. The two neonates whose cord blood were positive for CT DNA and survived at birth developed early onset neonatal sepsis. The finding of the present study showed trans-placental CT infection is associated with stillbirth (p<0.001) OR 38.5, 95% CI (6.91- 412.3). Neonates whose cord blood were positive for CT DNA were more likely to be stillborn than those with cord blood negative for CT DNA.

A prevalence of 5.6% of CT infection among pregnant women in the study area is high but slightly lower than what has been reported from other parts of sub-Saharan Africa. A pooled prevalence rates of 6.9% and 6.1% were reported for East and Southern Africa and, West and Central Africa respectively (5, 6)

Vertical transmission of CT and its consequential impact on the infected mother and the neonate has been reported by some studies (14, 15). Studies on the stages of pregnancy at which vertical transmission of the infection occurs are scarce and not well defined. The present study observed trans-placental transmission of CT from the infected mother to the fetus. Cord blood was positive for CT DNA in 11 out of 112 (10.18%) neonates screened. The findings of the present study is similar to 10.34% reported elsewhere (16).

Maternal infections are important causes of stillbirth, accounting for half of stillbirths in low and middle-income countries and 10–25% in high-income countries. Some studies have suggested that infections in general may account for up to 10–66% of miscarriages and these risks for miscarriages are higher in pregnant women in low- and middle-income countries (15, 17, 18).

Earlier studies reported spontaneous abortion and stillbirth among mothers with CT infection (7). CT DNA was observed to be more common in products of conception and the placenta in women with miscarriage than in their control counterparts (15). Miscarriage, stillbirth and ectopic pregnancy were reported to be higher in CT infected pregnant women than their uninfected counterparts (10, 19, 20). One such study found CT antibodies in 33.3% of mothers with stillbirths in comparison to 10.4% of mothers with live births (? < 0.05).

The mechanism by which CT infection may lead to adverse outcomes of pregnancy is not clearly understood. It was suggested that CT may infect the fetus, triggering a harmful inflammatory response with cytokine release leading to miscarriage, premature rupture of membranes, or preterm labor. It could also possibly be caused by maternal inflammatory response that induces embryonic rejection due to homology of the chlamydial and human 60 kDa heat shock proteins (21, 22). Some studies have suggested that this pathogenic

effect of CT infection may also play an important role in stillbirths (7, 23). CT antibodies were reported to be higher in mothers who had stillbirths compared to mothers with live births(4, 7, 24-26).

Despite substantial burden of CT infection on preterm birth estimated for sub-Saharan Africa and Asia, few published studies of CT infection and related outcomes of preterm labor and/or low birthweight from countries in these regions exist. Among the studies that could be identified, the majority seem to support a role for CT infection in preterm birth and similar pregnancy outcomes (27).

Stillbirth in the present study was 11 out of 112 (10.18%) of which nine(9) were attributable to transplacental transmission of CT from the infected mother to the fetus. Other routes of perinatal transmission: intrapartum or postpartum have been implicated in neonatal morbidity and mortality (28). Earlier studies reported septicemia, conjunctivitis, pneumonia, gastritis and urinary tract infection as documented neonatal sepsis among neonates of CT infected mothers (25, 29) .

Nine (9) out of the eleven (11) neonates whose cord blood were positive for CT DNA were stillbirths. The two live-birth neonates with CT DNA positive cord blood had early onset neonatal sepsis. It is therefore, clear that intrauterine transmission of CT is associated with high perinatal morbidity and mortality.

Prevention of adverse maternal and perinatal outcomes in CT infected pregnant women has been impeded for two primary reasons: lack of an effective human vaccine and progressive targeted screening/treatment recommendations for pregnant women (27).

Risk factors for adverse pregnancy outcome in CT infections have been reported by several studies (4, 15, 24, 30). These risk factors have been used to identify individuals at risk for prophylactic antibiotics (10).

Selection of antibiotics for the management of CT in pregnancy required the use of antibiotics which have proven to be of low toxicity to both the mother and fetus.

The use of such antibiotics in prophylactic management in at-risk pregnant women was reported to reduce the impact of CT infection in pregnancy on both the infected mother and neonate (29).

Earlier studies observed a significantly lower rates of CT infection for neonates born to women who received treatment with erythromycin as opposed to those who were not treated for CT. Antibiotic prophylaxis though effective in preventing adverse effect of CT infection in pregnancy where routine screening is not done, that is not part of the ANC service in Ghana. It will therefore not be out of place, to suggest the inclusion of prophylactic antibiotics in ANC services since the facilities do not have the capacity for routine screening.

Despite the fact that effective diagnoses and management of CT infection in pregnancy is able to reduce the impact of the infection on maternal and perinatal outcomes, CT management in Ghana is syndromic and has the ability to detect between 30 to 80% of infections (31). The low case detection rate is attributable to the fact that most of the cases are asymptomatic and would not present for management. They are most often diagnosed when the individual presents to the health facilities for reasons other than CT infection. The gold standard of routine screening for CT as part of ANC services should be part of the medium to long term plans of maternal and child health goals not only Ghana but other countries in Sub-Sahara Africa. Lack of human resource and equipment has been a major challenge. This therefore, would require a major policy direction at the national level for most developing countries.

Conclusion

The present study identified high prevalence of CT infection among pregnant women in the Central Region of Ghana. Trans-placental transmission of CT from an infected mother to the fetus has been established in the study and is associated with stillbirth and early onset neonatal sepsis. Considering the fact that screening of pregnant women for CT is not available in Ghana and most developing countries, it is recommended that at-risk pregnant women should be identified and provided with prophylactic antibiotics to prevent maternal morbidity and mortality due to CT infection and the impact of vertical transmission on the fetus. It is also suggested that routine screening for CT infection for all pregnant women be made part of ANC service for developing countries as part of medium to long term health policy.

Declaration of Conflict of Interest

We declare no potential conflict of interest with respect to the conduct of the research and/or the publication of this article.

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We received no financial support for the conduct of the research and/or the publication of this article. The research was founded by contributions from the principal investigator.

Ethical consideration.

We adhered strictly and completely to all protocols and standards with respect to the conduct of research involving human subjects according to the Helsinki Declaration. The study was approved by the Institutional Review Board of the University of Cape Coast.

Authors Contributions

MS and SDB conceptualized and designed the study and the data collection tool and supervised the collection of data entry and analysis. Laboratory analysis was supervised by MS and HO. MS JCM, HO and SDB prepared the first draft. MS, SDB and JCM finalized the manuscript for publication.

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