Erythromycin versus amoxicillin for the management of chlamydia infection in pregnant women: a randomized controlled trial

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ABSTRACT

Background: Chlamydia infection in pregnancy is associated with perinatal and neonatal complications like prelabour rupture of membranes, preterm birth, low birth weight, neonatal inclusion conjunctivitis and neonatal pneumonia. Aim: The aim of the study was to compare the efficacy and tolerability of erythromycin with amoxicillin in the management of Chlamydia trachomatis infection in pregnant women. Methods: Two hundred and twenty pregnant women that were positive to the rapid Chlamydia antigen test were randomized to receive either amoxicillin or erythromycin for one week at the antenatal clinics of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife. Their partners were treated with doxycycline for 1 week and barrier contraception was used by the couples during the treatment. The subjects were re-screened four weeks after enrolment. Data was analyzed with SPSS version 20 and \( P \)-value <0.05 was taken as statistically significant. Results: The microbiological clearance rates were 93.2% and 97% for Amoxicillin and Erythromycin respectively. The difference was however not significant (Exact 1.60, \( p \)=0.33). The relative risk was 0.96; 95% CI 0.9-1.0. There was also no statistically significant difference in occurrence of side effects. \( (\chi^2=1.38; \ P = 0.28) \) and drug discontinuation rates. Conclusion: Amoxicillin was comparable to erythromycin for the treatment of antenatal Chlamydia trachomatis infection. The drug discontinuation rates and occurrence of side effects were similar. Therefore, amoxicillin is an effective alternative for treatment of antenatal Chlamydial infection when there is significant side effect with the use of erythromycin.

Key words: Chlamydia, erythromycin, amoxicillin, efficacy, microbiological clearance rates, side effects
INTRODUCTION

Annually, 92 million new cases of Chlamydia infection occur globally; and 3 million new cases occur annually in the United States of America.\(^1\) The reported prevalence of this infection among pregnant women ranges from 5% to 26% depending on the population being studied.\(^2\) Antenatal Chlamydia infection has been associated with adverse perinatal outcomes such as low birth weight, prelabour rupture of membranes, preterm birth and stillbirth.\(^3\) It has been estimated that each year, over 155,000 infants are born to women infected with \textit{Chlamydia trachomatis}. The vertical transmission of \textit{Chlamydia trachomatis} can result in conjunctivitis or pneumonia in up to 50% or 20% of exposed infant respectively.\(^4\) In Nigeria, prevalence of 13.3% was reported in Benin City in 2005\(^5\) while 11% was reported in Abeokuta in 1989.\(^6\) The diagnosis and treatment of Chlamydia infected women before delivery have been shown to significantly lower the risk of these perinatal morbidities and neonatal infections.\(^5,6\)

Treatment options for \textit{Chlamydia trachomatis} infection in pregnancy include erythromycin, azithromycin, clindamycin and amoxicillin. Erythromycin is the drug of choice in pregnancy but it has a lot of side effects especially gastrointestinal that limits the patient’s compliance and thereby reducing treatment effectiveness.\(^7\) The common side effects of erythromycin are anorexia, nausea, vomiting and diarrhoea.\(^8\) Gastrointestinal intolerance due to direct stimulation of gut motility is the most frequent reason for discontinuing the drug.\(^9\) Azithromycin is equally an effective drug; it is given as a single dose and therefore enhances patient’s compliance. It is however costly when compared to other drugs; and therefore limits its use in low resource settings like ours. Clindamycin and amoxicillin are presently being evaluated as substitute for Erythromycin as they appear to be safer alternatives to erythromycin because of reduced side effects. Many studies have been carried out to compare the effectiveness of these drugs. However, most of these studies were done outside this environment.\(^9,10\) The World Health Organization thereafter advocated for more research about appropriate intervention for this infection in the developing World. The aim of this study was to compare the efficacy and tolerability of erythromycin with amoxicillin in the management of \textit{Chlamydia trachomatis} infection in pregnant women.

METHODOLOGY

Trial design
This was a randomized controlled trial, parallel groups, ratio 1:1.

Informed consent
Informed consent was obtained from all the patients. This trial was registered at clinicalTrials.gov in September 2013. The registration number was NCT01946256.

Participants
Eligibility criteria for this study were pregnant women between the gestational ages of 13 weeks and 36 weeks, had positive Chlamydia trachomatis antigen test and ability to comply with the follow-up process. However, women with low lying placenta or placenta praevia; and those that had history of allergy to any of the drugs were excluded.

The study was carried out at the two tertiary health care units of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife; the Wesley Guild Hospital and Ile Hospital unit. Ethical approval was obtained from the Ethics and Research Committee of the institution. The Ethical clearance certificate number was ERC2013/09/06. This trial was registered at clinicalTrials.gov in September 2013. The registration number was NCT01946256. Participants were recruited from the antenatal clinics of these hospitals from October 2013 to March 2014. Each participant was counselled about the study and informed consent was obtained. Socio-demographic, sexual behaviour and other information were obtained from each woman and this was entered into a proforma designed for the study.

Endocervical swabs were collected from 1684 pregnant women and the samples were processed with One Step Chlamydia rapid test kit manufactured by Span Biotech limited, Hong Kong,\(^11\) a rapid immunoassay for direct
qualitative detection of *Chlamydia trachomatis* antigen in endocervical swab specimen. Antibody specific to *Chlamydia trachomatis* antigen are coated in the test region. During testing, the extracted antigen solution reacts with an antibody to *Chlamydia trachomatis* that is coated with particles and generates coloured line in the test line region. According to the manufacturer, the sensitivity and specificity of the test kit are 96.5% and 99.3% respectively. Two hundred and twenty women that were positive to the test kit were then randomized into either of the study group.

**Interventions**
Participants randomized to the study group received amoxicillin; one capsule three times daily for seven days. Patients randomized to the control group received erythromycin; one caplet four times daily for seven days. Study drugs were dispensed by the principal investigator. The sexual partners were treated with Doxycycline: one capsule twice daily for one week and counseled to use barrier contraception for that week. The drugs administered were taken with food and a full glass of water; fruit juice was discouraged. The couples were given drug cards to document compliance and side effects. The study’s proforma was then filled for each participant. The women were also contacted through mobile telephone calls during the treatment to enhance compliance. The investigator’s phone number was also provided on the drug cards for contact at any time.

Telephone calls were made to the patients during the treatment to enhance compliance. The drug cards were collected four weeks after allocation. The patients were re-screened four weeks after allocation to check for clearance of the infection using the chlamydia screening kit as described above. Those that were still positive after the treatment were treated with azithromycin.

**Outcomes**
The primary outcome was microbiological clearance after completion of medications and the secondary outcomes were occurrence of side effects and drug discontinuation rates. Microbiological clearance was determined by a repeat rapid Chlamydia antigen test on endocervical swab.

**Sample size**
The sample size was calculated using the formula for comparison of proportion. A study in Houston found a test of cure of 96% in the erythromycin group. The sample size was calculated accepting a study power of 80%, confidence interval of 95%, a study to control ratio of 1:1, an acceptable attrition rate of 20%, and with the aim of achieving a 13% minimum detectable difference in the test of cure between these two drugs, sample size of 110 participants was calculated for each arm.

**Randomization sequence generation**
Participants were allocated to one of the two treatment groups according to computer generated randomization sequence generated by a statistician. Block randomization was used in order to keep the sizes of treatment groups similar. They were randomized in blocks of 20.

**Allocation concealment mechanism**
Allocation concealment was ensured by the use of sequentially numbered opaque envelopes.

**Implementation**
The statistician generated the random allocation sequence while the investigators enrolled and assigned the participants to interventions.

**Blinding**
Blinding was not done because the drugs were not similar in formulation and dosage.

**Statistical analysis**
Data was analyzed by Statistical Package for Social Sciences version 20 and *P*-value <0.05 was taken as statistically significant. Independent T-test was used to compare the baseline characteristics between the two groups while chi-square or Fisher’s Exact test was used to compare the outcome variables. Relative risk and absolute risk difference was also generated for the outcomes.

**RESULTS**
During the study period (October 2013 to March 2014), one hundred and ten women were allocated into each group (figure 1). Two women were not allocated because they could
not meet up with the follow up schedule after the initial screening. Two hundred and four women that completed the study per protocol were analyzed according to the assigned group. Four women (3.6%) were lost to follow up in the amoxicillin group while nine (8.2%) were lost to follow up in the erythromycin group. However, 3 participants (2.7%) in the Amoxicillin group delivered before the test for microbiological clearance; one out of which was a preterm delivery while the remaining two women delivered at term. Only one participant (0.9%) in the erythromycin group discontinued medications due to severe abdominal pain. The study was concluded after the sample size was completed.

Figure 1: Participants’ flow chart for the Randomized Controlled Trial of amoxicillin and erythromycin for treatment of antenatal chlamydia infection

1682 pregnant women were screened for Chlamydia trachomatis infection using the rapid antigen test kit.

1462 women were excluded
1460 women were negative
2 women were unable to meet up with follow up plan

220 women were randomized

110 women were allocated to Amoxicillin
110 women received Amoxicillin

4 women were lost to follow up
3 women delivered before the repeat test
Excluded from analysis

103 women were included in per protocol analysis

110 women were allocated to Erythromycin
110 women received Erythromycin

8 women were lost to follow up
1 woman discontinued drug due to side effects
Excluded from analysis

101 women were included in per protocol analysis

Table 1: Comparison of the baseline characteristics of the study participants between the two groups

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Amoxicillin N=103 Mean ± SD</th>
<th>Erythromycin N=101 Mean ± SD</th>
<th>Mean difference</th>
<th>T statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29.32± 4.75</td>
<td>28.98± 5.23</td>
<td>0.34</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>Parity</td>
<td>1.03± 1.15</td>
<td>1.0± 1.13</td>
<td>0.03</td>
<td>0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>Gestational</td>
<td>28.66± 5.70</td>
<td>29.36±4.59</td>
<td>0.70</td>
<td>1.00</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Table 2: Per protocol analysis of the outcome measures of erythromycin versus amoxicillin for treatment of antenatal *Chlamydia trachomatis* infection

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Amoxicillin N=103 Frequency (%)</th>
<th>Erythromycin N=101 Frequency (%)</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test of Microbiological clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>96 (93.2)</td>
<td>98 (97.0)</td>
<td>1.60</td>
<td>0.33</td>
</tr>
<tr>
<td>Positive</td>
<td>7 (6.8)</td>
<td>3 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>94 (91.3)</td>
<td>88 (87.1)</td>
<td>1.38</td>
<td>0.28</td>
</tr>
<tr>
<td>Present</td>
<td>9 (8.7)</td>
<td>13 (12.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Calculated using Fisher Exact test

Table 3: Effect size and precision of outcomes between the two groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amoxicillin N=103 Frequency (%)</th>
<th>Erythromycin N=101 Frequency (%)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Absolute Risk Difference(95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological clearance</td>
<td>96 (93.2)</td>
<td>98 (97.0)</td>
<td>0.96 (0.90-1.02)</td>
<td>-0.04 (-0.32-0.14)</td>
</tr>
<tr>
<td>Occurrence of side effects</td>
<td>9 (8.7)</td>
<td>13(12.9)</td>
<td>0.68 (0.14-3.28)</td>
<td>-0.04 (-0.11-0.02)</td>
</tr>
</tbody>
</table>
Baseline data
The baseline characteristics of the participants were comparable between the two groups as shown in table I. The mean difference between the ages of both groups was 0.34, $P = 0.58$. The mean difference in their parities was 0.03, $P = 0.86$ and the mean difference between the gestational ages was 0.70, $P = 0.32$.

This study was analyzed per protocol. The microbiological clearance rates of Amoxicillin and Erythromycin were 93.2% and 97% respectively. These were shown in table 2. The proportion of those with microbiological clearance is higher in the Erythromycin arm but the difference was not statistically significant (Exact $= 1.60; P = 0.33$).

The occurrence of side effects was also comparable between the two groups. Erythromycin group had the higher proportion of patients with side effects but the difference was not statistically significant ($X^2=1.38; P=0.28$). The side effects evaluated in this study were vomiting, abdominal pain and body weakness. The commonest side effect was abdominal pain which occurred more in the erythromycin arm. Abdominal pain occurred in 6 (5.9%) participants in the erythromycin arm and 3 (2.9%) in the amoxicillin arm.

Within the study period, 30 women in the amoxicillin group delivered with mean birth weight of 3.19kg and 38 women in the erythromycin group delivered with mean birth weight of 3.32kg. These could not be compared because the remaining women were yet to deliver at the conclusion of the study.

The relative risk of microbiological clearance was 0.96, 95% CI 0.90 - 1.02 while the absolute risk difference was -0.04, 95% CI -0.32 to 0.14 (table 3). The relative risk for the occurrence of side effects was 0.68, 95% CI 0.14-3.28 and risk difference was -0.04, 95% CI -0.11-0.02. The number to treat for microbiological clearance and occurrence of side effects were 27 and 26 respectively (table 3).

The difference between the partners' compliance with use of Doxycycline to treat a concurrent infection in the sexual partners was also not significant ($X^2=0.01; P=0.90$). Seventy nine percent of the partners were compliant with the use of doxycycline in the amoxicillin group while 80.2% were compliant in the Erythromycin group. However, there is a statistically significant difference in the use of barrier contraception between both groups ($X^2 = 5.53; P=0.02$). The proportion of the partners that were compliant with use of barrier contraception for amoxicillin and erythromycin arms were 65 and 44.6% respectively (table 4).

Harms
No harm was reported during the study period.

DISCUSSION
The baseline characteristics of the participants were comparable. This showed that randomization was largely successful. There were no statistically significant differences in the age, estimated gestational ages and parities between the two groups. Therefore, the likelihood that these factors would affect the results has been eliminated. Treatment efficacies of 82-98% have been reported for amoxicillin in the treatment of antenatal Chlamydia trachomatis infection in several studies. A study by Magat et al. reported success rates of 72.3% and 84.6% for erythromycin and amoxicillin group respectively; this difference was also statistically significant. Rahangdale et al. also reported clearance rates of 97%, 95% and 64% for azithromycin, Amoxicillin and erythromycin in the treatment of antenatal Chlamydia infection in an observational cohort study. Turrentine et al. reported very high cure rates of 96%, 94% and 98% with erythromycin, amoxicillin and clindamycin respectively for treatment of antenatal Chlamydia trachomatis infection. The difference between the three drugs was also not statistically significant. These high cure rates may be attributed to concurrent treatment of the sexual partners and the use of barrier contraception during the treatment. This has minimized the risk of re-infection. The microbiological clearance rates in this study were comparable to the rates reported by Turrentine. This was due to the fact that the sexual partners were also treated with doxycycline and barrier contraception was
The finding of this study about the microbiological clearance of both drugs was therefore similar to other randomized trials that compared the efficacy of amoxicillin with erythromycin for treatment of antenatal Chlamydia trachomatis infection. There were differences in the efficacy of the drugs but the differences were not statistically significant. This could be due to the sample size. The sample size used for these trials is within the same range; about 100 women were randomized into each group.

The difference in the side effects reported in this study was also not statistically significant. The proportion of participants that had side effects was higher in the erythromycin arm; 8.7% of women in the amoxicillin arm of the trial and 12.9% of those in the erythromycin arm of the trial developed side effects in the course of treatment. Side effects were usually more in the erythromycin groups in many studies. The study by Alary et al. reported a statistically significant difference in the side effects of both drugs. Amoxicillin had a side effect rate of 31% while erythromycin had a side effect rate of 6%. According to Magat et al., 46.1% of women in the erythromycin arm and 7.7% of those in the amoxicillin developed side effects during the course of treatment; and the difference was statistically significant. Turrrentine et al. also reported a statistically significant difference in occurrence of side effects. The difference between this study and other studies in respect of occurrence of side effects may be due to the fact that this study was not blinded.

None of the participants in the amoxicillin arm discontinued her medications. Only one participant discontinued the medications in the erythromycin arm on account of severe abdominal pain. The difference between the two groups was also not significant. The risk of occurrence of side effects was also reduced by 32% with the use of amoxicillin, it was not statistically significant and the confidence interval was wide. This indicated that a larger sample size will be needed to detect a significant difference in the occurrence of side effects between the two groups. Also, 25 women would have to be treated with amoxicillin in order to prevent occurrence of side effect in a woman treated with erythromycin. This study was not blinded although strict allocation concealment was ensured by the use of sequentially numbered opaque envelopes through the statistician. Also, Polymerase chain reaction would have been preferred for diagnosis.

CONCLUSION

Amoxicillin was comparable to erythromycin for the treatment of antenatal Chlamydia trachomatis infection. The drug discontinuation rates and occurrence of side effects were similar. Therefore, Amoxicillin is an effective alternative for treatment of antenatal Chlamydial infection when there is significant side effect with the use of erythromycin. A large multicentre randomised controlled trial is however necessary to detect more subtle differences between amoxicillin and erythromycin for treatment of antenatal Chlamydia trachomatis infection. Such study should use a large sample size in order to detect little difference in the efficacy and tolerability of both drugs.

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REFERENCES

4. Ogiogwa IO, Motayo BO, Okerentugba PO, Innocent-Adielle HC, Tafeng Y, Onoh CC, Nwanze JC, Okonko IO. Detection of Chlamydia trachomatis antigen among...


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