Factors associated with infection following operative vaginal birth – a secondary analysis of the ANODE randomized controlled trial

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Factors associated with infection following operative vaginal birth – a secondary analysis of the ANODE randomized controlled trial

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Trial Registration
ISRCTN11166984

Data sharing
De-identified participant data will be shared in accordance with the National Perinatal Epidemiology Unit Data Sharing policy. Requests for access to the data will be considered by the National Perinatal Epidemiology Unit Data Sharing committee from the date of publication. Data will be shared after approval of a proposal with investigator approval and completion of a signed data sharing agreement. The trial protocol, statistical analysis plan, and other study documents are also available on request through this route. Access to the data can be requested from general@npeu.ox.ac.uk.

Word Count
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Main text 3000

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Condensation page

Condensation

Factors associated with infection following operative vaginal birth using a secondary analysis of the ANODE randomized controlled trial.

Short Title: Factors associated with infection following operative vaginal birth

AJOG at a Glance

A. Why was this study conducted?

• The ANODE randomised controlled trial demonstrated the benefit of prophylactic antibiotic following operative vaginal birth.

• However, there was a high burden of infection in ANODE despite prophylactic antibiotics.

• It was unclear whether the protective effect of prophylactic antibiotic was limited to women who underwent episiotomy.

B. What are the key findings?

• Prophylactic antibiotic appears to protect against infection in all women who have perineal trauma following operative vaginal birth.

• Risk factors for infection include the use of episiotomy, forceps, primiparity, overweight and timing of antibiotic administration.

C. What does this study add to what is already known?

• Prophylactic antibiotics should be given to all women who have operative vaginal births as soon as possible after they have given birth.

• This study has identified additional risk factors for infection following operative vaginal birth, which have the potential to be modified.
Abstract

Background: The recent ANODE randomized controlled trial showed that women allocated prophylactic intravenous amoxicillin and clavulanic acid had a significantly lower risk of developing confirmed or suspected infection within 6 weeks of operative vaginal birth. Some international and national guidelines have subsequently been updated to include prophylactic antibiotics after operative vaginal birth. However, the generalizability of the ANODE results may be limited in settings where episiotomy rate is lower (89% of women in ANODE had an episiotomy). Additionally, there was a high burden of infection in ANODE despite prophylactic antibiotic. It is essential to identify modifiable risk factors for infection after operative vaginal birth including timing of antibiotic administration.

Objectives: This study aimed to evaluate if the effectiveness of the prophylactic antibiotic in reducing confirmed or suspected infection was independent of perineal trauma, identify risk factors for infection after operative vaginal birth and investigate variation in efficacy with timing of antibiotic administration.

Study design: This study was a secondary analysis of 3225 women with primary outcome data from the ANODE randomized controlled trial. Women were divided into subgroups according to the perineal trauma experienced (episiotomy and/or perineal tear). The consistency of the prophylactic antibiotics in preventing infection across the subgroups was assessed using log binomial regression and the likelihood ratio test.

Multivariable log binomial regression was used to investigate factors associated with infection. The multivariable risk factor model was subsequently fitted to the group of
women who received amoxicillin and clavulanic acid to investigate the timing of antibiotic administration.

Results: Of the 3225 included in the secondary analysis, 2144 (66.5%) had an episiotomy alone, 726 (22.5%) had an episiotomy and a tear, 277 (8.6%) had a tear alone and 78 (2.4%) had neither episiotomy nor tear. Among women who experienced perineal trauma, amoxicillin and clavulanic acid was protective against infection in all subgroups compared to placebo with no significant interaction between subgroup and trial allocation (p=0.17).

2925 women were included in the multivariable risk factor analysis. Episiotomy was associated with an adjusted risk ratio of infection of 2.94 (95% confidence interval 1.62-5.31), forceps 1.37 (95% confidence interval 1.12-1.69) compared to vacuum extraction, primiparity 1.34 (95% confidence interval 1.05-1.70), amoxicillin and clavulanic acid administration 0.60 (95% confidence interval 0.51-0.72), body mass index 25-29.9 kg/m$^2$ 1.21 (95% confidence interval 1.00-1.47) and body mass index $\geq$30 kg/m$^2$ 1.22 (95% confidence interval 0.98-1.52) compared to body mass index <25 kg/m$^2$. Each 15-minute increment between birth and antibiotic administration was associated with a 3% higher risk of infection (adjusted risk ratio 1.03, 95% confidence interval 1.01-1.06).

Conclusion: Timely prophylactic antibiotics should be given to all women after operative vaginal birth, irrespective of type of perineal trauma. The use of episiotomy, forceps, primiparity and overweight are associated with an increased risk of confirmed or suspected infection following operative vaginal birth.

Key words – amoxicillin and clavulanic acid, confirmed or suspected infection, episiotomy, forceps, vacuum extraction, operative vaginal birth, prophylactic antibiotics
Introduction

Sepsis remains a major cause of maternal deaths globally, accounting for around 5% in high income and 11% in low income countries. The World Health Organization Global Maternal Sepsis Study reported that for every woman with a severe maternal outcome (death or near miss) attributed to infection, a further seven pregnant or recently pregnant women were hospitalized with an infection. An increased risk of sepsis in association with caesarean section birth has been recognized for many years, and more recently for operative vaginal birth (OVB) (forceps or vacuum extraction). Based on substantial randomized controlled trial evidence of effectiveness, including data from a recent large trial of antibiotic prophylaxis after OVB, prophylactic antibiotics for both procedures are now indicated and have been incorporated into some national and international guidelines. Although the use of operative vaginal birth has decreased in many countries, it remains an important obstetric practice, particularly in settings where access to obstetric care may be limited.

The ANODE trial (ISRCTN11166984) reported that women allocated amoxicillin and clavulanic acid had a statistically significantly lower rate of confirmed or suspected infection (11%, n=180/1619) than women allocated placebo (19%, n=306/1606) (risk ratio (RR) 0.58, 95% CI 0.49-0.69, p<0.001). Nevertheless, the 11% infection rate among women receiving antibiotics indicates that identifying and tackling other modifiable risk factors remains vital in reducing the burden of maternal infection in women who have OVB. Almost 90% of women in ANODE had an episiotomy which may limit generalizability to settings where the episiotomy rate is lower, and antibiotics were administered up to six hours after women gave birth. Previous
studies have found the use of episiotomy is significantly associated with infection up to 8 weeks following birth for all birth modalities. On this basis, prophylactic antibiotic is not recommended in a recently updated ACOG Practice Bulletin. Determining whether the benefit of amoxicillin and clavulanic acid is independent from perineal trauma status (perineal tear and/or episiotomy) is therefore essential. Evaluation of timing of prophylactic antibiotic administration is needed to direct guidelines which currently do not have a specified administration time.

The primary objectives of this secondary (post-hoc) analysis of the ANODE trial were therefore to: (1) evaluate if the efficacy of the prophylactic amoxicillin and clavulanic acid in reducing confirmed or suspected infection was independent of perineal tear and episiotomy; (2) identify risk factors for confirmed or suspected infection among women who have operative vaginal birth and determine the population attributable fraction, and (3) investigate the optimum timing of prophylactic amoxicillin and clavulanic acid administration to minimize risk of confirmed or suspected infection.
Methods

Study population
Between March 13th 2016 and June 13th 2018, 3427 women who underwent a forceps or vacuum assisted birth at 36 weeks or greater gestation were randomly assigned (1:1) to receive a single intravenous dose of prophylactic amoxicillin and clavulanic acid or placebo as soon as possible after birth, and no more than 6 hours later. This secondary analysis included all women in the ANODE trial cohort except for those with missing primary outcome data (n=195) and those who withdrew consent (n=7).

Exposure assessment
Maternal obstetric and demographic data were collected from clinical records at trial entry by a research midwife, and entered into electronic case report forms in an OpenClinica database. The height and weight measurements used for this analysis were those first recorded for the current pregnancy, which largely corresponded to the first contact with obstetric services. The risk factors (for infection) included were based on previous literature, and their availability in the dataset (Appendix Table S1).

Outcome Assessment
The primary outcome was confirmed or suspected maternal infection within 6 weeks of birth, defined by either:

- A new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic
features (pyelonephritis or sepsis) or other systemic infection (clinical sepsis),

or

- Confirmed systemic infection on culture, or

- Endometritis as defined by the US Centers for Disease Control and Prevention.¹⁵

The primary outcome was ascertained from medical records at hospital discharge and by a telephone interview at six weeks post-birth, following which women were sent a questionnaire for collection of data on secondary outcomes.⁵

**Statistical analysis**

**Subgroup analysis of infection by perineal trauma**

Women were divided into subgroups according to the perineal trauma experienced during the OVB: solely a perineal tear, solely an episiotomy, both a perineal tear and an episiotomy and neither perineal tear nor episiotomy. Perineal tears included both first and second degree tears.

The consistency of the effect of amoxicillin and clavulanic acid in preventing confirmed or suspected infection compared to placebo was assessed across perineal trauma subgroups using log binomial regression. Risk ratios and 95% confidence intervals are presented for each subgroup. Likelihood ratio testing was used to assess statistical interaction.
Risk factors for infection: both trial arms

Women with missing baseline data were excluded from the risk factor analysis.

Women were categorized by the most invasive mode of OVB that was attempted, with forceps classed as more invasive than vacuum extraction. The reasons for OVB were classed as “time-critical” and “non-time critical” based on clinical judgement, as aseptic techniques may have been compromised in “time-critical” situations.

The characteristics of the study population were summarized by presence or absence of confirmed or suspected infection, with numbers (and percentages) presented for binary and categorical variables with comparison by Chi-squared tests of association, means (with standard deviations) for normally distributed continuous variables with comparison by Student’s T test and medians (with interquartile ranges) with comparison by Wilcoxon Rank Sum for non-normally distributed continuous data.

All factors that had a p-value <0.2 in univariable analysis were included in the initial multivariable log binomial regression model. A backwards elimination approach was used to select variables for the final model to avoid overfitting and selection bias, and to provide correct estimates of standard error. Where there was significant pre-existing evidence of association, an a priori decision was taken to retain specific variables in the model; these included mode of birth, trial allocation and body mass index (BMI) category. Likelihood ratio testing was used to establish whether additional variables significantly contributed to model fit. Overall model fit was assessed by Akaike’s Bayesian information criterion and Schwarz’s Bayesian
information criterion. Collinearity between variables used in the multivariable analysis was tested using Spearman correlation with a value of 0.8 considered significant.

Based on biological plausibility, statistical interaction was tested for episiotomy and mode of birth due to the more invasive nature of forceps over vacuum extraction. The interaction between the use of episiotomy and BMI was also tested, as BMI has been found to be associated with episiotomy use.

A sensitivity analysis was undertaken using multiple imputation for missing baseline characteristics for the multivariable risk factor model. 300 participants had some missing baseline data. Parity, mode of birth and episiotomy were found to be significant predictors of “missingness” using univariable log binomial regression, suggesting the data were likely to be missing at random. All baseline variables in Table 1 were included in the imputation model, using the method of predictive mean matching due to the non-normal distribution of variables. Ten imputations were performed, and the previous multivariable model was then fitted to this multiple imputation dataset.

Risk factors for infection and timing of administration: amoxicillin and clavulanic acid arm only

To reflect current recommended clinical practice of amoxicillin and clavulanic acid after OVB, subsequent analyses were restricted to the 1453 women who received amoxicillin and clavulanic acid. The final multivariable log binomial risk factor model was fitted to this group of women and timing of antibiotic administration was added to the model, categorized as 15-minute intervals to aid clinical interpretation.
To determine the population attributable fraction for each identified adjusted risk factor, Miettinen's formula was utilized.\textsuperscript{18}

All statistical tests used a significance level of 0.05 and analyses were completed using Stata Statistical Software version 16 (StataCorp, Tx).

Ethics committee approval

The ANODE trial was approved by the HRA NRES Committee South Central - Hampshire B (Study Ref:15/SC/0442). Further Research Ethics Committee approval was not required for this analysis of anonymized trial data.
Results

Subgroup analysis of infection by perineal trauma

3225 women with primary outcome data from the original trial were eligible for the perineal trauma subgroup analysis (Figure 1). The majority of women (2144; 66.5%) had an episiotomy only, 726 (22.5%) had both an episiotomy and a tear, and 277 (8.6%) had a tear only. Only 78 (2.4%) women had neither an episiotomy nor a tear.

The proportion of women who developed a confirmed or suspected infection increased with the extent of perineal trauma in both trial arms (Figure 2). There was no statistically significant difference in incidence of infection in the amoxicillin and clavulanic acid arm compared to the placebo arm among women who had no perineal trauma (RR 1.18, 95% CI: 0.11-12.49), noting the very limited power of this analysis. Among women who experienced perineal trauma, amoxicillin and clavulanic acid was protective against infection in all subgroups compared to placebo: tear only (RR 0.20, 95% CI: 0.04-0.87), episiotomy only (RR 0.66, 95% CI: 0.53-0.81) and episiotomy with tear (RR 0.50, 95% CI: 0.37–0.69) (Figure 2). There was no significant statistical interaction between perineal trauma subgroup and trial allocation on the risk of developing infection (p=0.17).

Risk factors for infection: both trial arms

Following the exclusion of those with missing baseline data, 2925 women were included in the multivariable risk factor analysis (Figure 1), of which 452 (15.5%) developed confirmed or suspected infection. Infection occurred a median of 7 days postnatal (IQR 4-11 days, data only available for 170/452). For women with systemic
Sepsis infection occurred a median of 5 days postnatal (IQR 3-8 days, data available for 15/15). The baseline demographic, obstetric and clinical characteristics of women who did and did not develop infection are presented in Table 1. All women included received either the placebo or amoxicillin and clavulanic acid intervention they had been allocated to at randomization. Factors associated with developing infection in univariable analysis were: maternal BMI (median 25.1 versus 24.5 kg/m², p=0.019), primiparity (85.0% versus 78.1%, p<0.001), forceps birth (76.5% versus 65.0%, p<0.001), episiotomy (97.6% versus 90.7%, p<0.001), receipt of amoxicillin and clavulanic acid (36.9% versus 52.0%, p<0.001), multiple modes of OVB attempted (6.4% versus 4.4%, p=0.071), and time critical reason for OVB (47.1% versus 52.1%, p=0.052).

Neither time-critical reason for OVB, nor attempting multiple modes of OVB contributed to model fit. The final model is shown in Figure 3a. Use of episiotomy (risk ratio (RR) 2.94, 95% CI 1.62-5.31) and use of forceps (RR 1.37, 95% CI 1.12-1.69) were significantly associated with infection. Receipt of amoxicillin and clavulanic acid was protective (RR 0.60, 95%CI 0.51–0.72). Compared to BMI category <25kg/m², the risk for women in BMI category 25-29.9kg/m² was statistically significantly increased (RR 1.21 (95% CI 1.00-1.47), but not for women in BMI category ≥30kg/m² (RR 1.22 (95% CI 0.98-1.52)). No significant interactions were found between mode of birth and episiotomy (p=0.345), or episiotomy and BMI (p=0.961).

The imputed data minimally changed the final multivariable risk factor model with all risk ratios for infection differing by under 5% (Appendix Figure S2).
Risk factors for infection and timing of administration: amoxicillin and clavulanic acid arm only

The final multivariable risk factor model for infection restricted to women who received amoxicillin and clavulanic acid can be seen in Figure 3b, where the risk ratios are similar to the full cohort model. The population attributable fraction for infection associated with the use of episiotomy was 81.4%, 23.8% for primiparity and 22.1% for forceps use.

Women received the amoxicillin and clavulanic acid a median of 192 (IQR 135-270) minutes after birth. Timing was modelled as a continuous categorical variable, as a significant linear trend was found at univariable analysis (p=0.043) with no evidence of departure from linearity. The addition of the timing of the intervention to the final multivariable risk factor model can be seen in Appendix Table S2. Each additional 15-minute increment between birth and antibiotic administration was associated with a 3% (95%CI RR 1.01-1.06) higher risk of infection, when adjusting for BMI category, mode of birth, episiotomy and parity. A woman receiving the amoxicillin and clavulanic acid 3 hours post-birth had an almost 50% higher risk of infection (1.03^{12}=1.43), and receipt at 6 hours post-birth was associated with a two-fold higher risk (1.03^{24}=2.03) than a woman receiving antibiotic within 15 minutes.
Comment

Principal findings

Analysis of this large prospective cohort of women undergoing OVB suggests that prophylactic amoxicillin and clavulanic acid is protective against confirmed or suspected infection following perineal trauma whether or not an episiotomy is used. Nevertheless, episiotomy is confirmed as an important risk factor for developing infection within 6 weeks of OVB, conferring a 3-fold higher risk compared to women who do not have an episiotomy, with around 80% of cases on a population basis attributable to this factor. Other significant risk factors include the use of forceps compared to vacuum extraction, and primiparity, both associated with a 30-40% increased risk. There was also tentative evidence that a BMI $\geq 25$ kg/m$^2$ may result in an elevated risk. Importantly, findings from this study suggest that prophylactic amoxicillin and clavulanic acid should be administered as soon as possible after OVB, and that the longer the delay the greater reduction in the efficacy of the treatment.

Results in the Context of What is Known

Observational studies have reported the use of episiotomy is associated with a 1.4 to 10 fold higher odds of infection.$^{10-13}$ The results from the analysis presented here, showing a 3 fold increase in infection, most closely align with the results of a British cohort study of nulliparous women who had OVB, which found a 4 fold higher odds of perineal infection with episiotomy use, however the study was limited to 10 days postpartum.$^{13}$
Most observational studies assessing maternal infection have not categorized OVB by the instrument used, or have used women undergoing caesarean section as the reference group. A US retrospective cohort of over 6800 operative vaginal births reported an unadjusted relative risk of 2.7 for postpartum infection for forceps relative to vacuum extraction, whilst a review found that the absolute proportion of women who developed infection ranged from 50% to over 4 fold higher following a forceps birth compared to vacuum extraction. Evidence for the association of primiparity with infection is mixed, and may reflect lack of adjustment for confounders in some studies.

The association of postpartum infection with obesity has been consistently found by other observational studies where the odds of infection ranged from 29% higher for postpartum endometritis to over 2 fold higher for sepsis.

**Clinical implications**

Whilst no novel risk factors for infection have been identified by this study, it is the first time that the associations with increased risk have been demonstrated in this specific population of women undergoing OVB. With the exception of parity, all identified risk factors are potentially modifiable and thus these results have the potential to influence clinical practice and guidelines. Most importantly, the very clear association between earlier administration of amoxicillin and clavulanic acid and lower infection rates emphasizes the added benefit of administration as soon as possible after women have given birth.
Research implications

A Cochrane review on the role of prophylactic antibiotics in OVB has been updated to reflect the results of the ANODE trial, but noted the need for further randomized controlled evidence in low-income settings, where routine intravenous administration may not be possible. It is questionable whether such a trial would be considered ethical given the strong recommendation from the World Health Organization concerning the use of prophylactic amoxicillin and clavulanic acid. Nevertheless, identifying and targeting modifiable risk factors in low and middle income countries is crucial as they disproportionately bear the burden of maternal mortality, accounting for 94% of global deaths.

Strengths and limitations

The ANODE trial initially highlighted the previously unknown burden of maternal infection following OVB, and this secondary analysis has identified key risk factors and their relative importance. Primary outcome data were missing for only 5.7% of women and the large sample size allowed for reasonable statistical power to identify risk factors. Furthermore, the long duration of follow-up through the whole of the first postpartum six weeks and the comprehensive definition of maternal infection meant that the true incidence of infection was likely to have been captured. Many other observational studies have been limited by their lack of active follow-up, meaning cases of maternal infection may have been missed. As this was a post-hoc analysis, it cannot be ruled out that the study is statistically underpowered to detect variation in the association between subgroups. The analysis was also limited by the number of obstetric, clinical and demographic
factors that were recorded for the trial. There may therefore be other significant
predictors of infection, including past medical history, smoking and socio-economic
status which have been previously identified.\textsuperscript{4,11,19,20} It should also be noted that, for
the observational analysis, there may be residual confounding, including
confounding by indication, which may account for the observed results. As with many
trials, the women recruited to ANODE may not have been representative of the
general population. 14\% of the women in the secondary analysis of ANODE came
from a Black and Minority Ethnic background. However, in 2016-2018 at least 20\%
of maternities in England were to women from a minority ethnic background.\textsuperscript{27}

Conclusions

This study has found no evidence to suggest that prophylactic amoxicillin and
clavulanic acid is less protective against confirmed or suspected infection following
operative vaginal birth with perineal trauma in the absence of episiotomy, which
provides reassurance of the benefit of prophylactic antibiotic in settings where the
episiotomy rate is lower. Findings suggest that the use of episiotomy, forceps birth,
primiparity and possibly obesity are associated with an increased risk of postpartum
confirmed or suspected infection in women undergoing OVB. Importantly for clinical
practice, the burden of infection may be further reduced by timely administration of
the antibiotic to all women irrespective of the state of their perineum.
Acknowledgements
We would like to acknowledge the women who participated in the ANODE trial, the ANODE Collaborative Group, site principal investigators and research staff.

Author contributions
All authors designed this secondary analysis. AH conducted the analysis with support from LL and MK. AH wrote the first draft of the manuscript which was edited and critically revised for content by LL and MK. MK is study guarantor.

References


Table 1: Baseline demographic, obstetric and birth characteristics of participants by development of confirmed or suspected infection

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Developed infection (n=452)</th>
<th>Did not develop infection (n=2,473)</th>
<th>p-value</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's age at randomization (years)*</td>
<td>30.5 (5.1)</td>
<td>30.4 (5.4)</td>
<td>0.71</td>
<td>1.00 (0.99 - 1.02)</td>
</tr>
<tr>
<td>Gestational age at randomization†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age category (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>5 (10.0%)</td>
<td>45 (90.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-&lt;38 weeks</td>
<td>28 (16.5%)</td>
<td>142 (83.5%)</td>
<td></td>
<td>1.65 (0.67 - 4.04)</td>
</tr>
<tr>
<td>38-&lt;39 weeks</td>
<td>58 (17.9%)</td>
<td>266 (82.1%)</td>
<td></td>
<td>1.79 (0.75 - 4.25)</td>
</tr>
<tr>
<td>39-&lt;40 weeks</td>
<td>105 (16.9%)</td>
<td>518 (83.1%)</td>
<td></td>
<td>1.69 (0.72 - 3.94)</td>
</tr>
<tr>
<td>40-&lt;41 weeks</td>
<td>130 (14.0%)</td>
<td>801 (86.0%)</td>
<td></td>
<td>1.40 (0.60 - 3.26)</td>
</tr>
<tr>
<td>41-&lt;42 weeks</td>
<td>112 (15.2%)</td>
<td>625 (84.8%)</td>
<td></td>
<td>1.52 (0.65 - 3.55)</td>
</tr>
<tr>
<td>42+ weeks</td>
<td>14 (15.6%)</td>
<td>76 (84.4%)</td>
<td></td>
<td>1.56 (0.60 - 4.07)</td>
</tr>
<tr>
<td>Maternal ethnicity</td>
<td></td>
<td></td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>393 (15.7%)</td>
<td>2,115 (84.3%)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>BAME</td>
<td>59 (14.1%)</td>
<td>358 (85.9%)</td>
<td></td>
<td>0.90 (0.70 - 1.16)</td>
</tr>
<tr>
<td>Body Mass Index †</td>
<td>25.1 (22.6,28.7)</td>
<td>24.5 (21.9,28.2)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Maternal BMI category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25kg/m²</td>
<td>221 (14.0%)</td>
<td>1,360 (86.0%)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>25-29.9kg/m²</td>
<td>136 (17.0%)</td>
<td>665 (83.0%)</td>
<td></td>
<td>1.21 (1.00 - 1.48)</td>
</tr>
<tr>
<td>≥30kg/m²</td>
<td>95 (17.5%)</td>
<td>448 (82.5%)</td>
<td></td>
<td>1.25 (1.00 - 1.56)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Single pregnancy</td>
<td>450 (15.5%)</td>
<td>2461 (84.5%)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>2 (14.3%)</td>
<td>12 (85.7%)</td>
<td></td>
<td>0.92 (0.26 - 3.34)</td>
</tr>
<tr>
<td>Parity</td>
<td>Multiparous</td>
<td>Primiparous</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>Multiparous</td>
<td>68 (11.1%)</td>
<td>542 (88.9%)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Primiparous</td>
<td>384 (16.6%)</td>
<td>1,931 (83.4%)</td>
<td>1.49 (1.17 - 1.90)</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Timing of membrane rupture pre-birth (hours)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;24hrs</td>
<td>386 (15.2%)</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>53 (16.0%)</td>
</tr>
<tr>
<td>≥48 hours</td>
<td>13 (21.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induction of labor</th>
<th>0.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced</td>
<td>230 (16.0%)</td>
</tr>
<tr>
<td>Not induced</td>
<td>222 (14.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mode of birth</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum extraction</td>
<td>106 (10.9%)</td>
</tr>
<tr>
<td>Forceps</td>
<td>346 (17.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple modes of operative vaginal birth</th>
<th>0.071</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>423 (15.2%)</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (20.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for operative vaginal birth</th>
<th>0.052</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-time critical</td>
<td>239 (16.8%)</td>
</tr>
<tr>
<td>Time critical</td>
<td>213 (14.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Episiotomy during birth</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>No episiotomy</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Episiotomy</td>
<td>441 (16.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tear during birth</th>
<th>0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td>No perineal tear</td>
<td>301 (15.0%)</td>
</tr>
<tr>
<td>Perineal tear</td>
<td>151 (16.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perineal wound sutured</th>
<th>Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal wound sutured</td>
<td>452 (15.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suturing location</th>
<th>168 (16.3%)</th>
<th>863 (83.7%)</th>
<th>0.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating theatre</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Labor ward</td>
<td>284 (15.0%)</td>
<td>1,610 (85.0%)</td>
<td>0.92 (0.77 - 1.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suture material</th>
<th>15 (14.9%)</th>
<th>86 (85.1%)</th>
<th>0.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vicryl</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vicryl Rapide</td>
<td>427 (15.7%)</td>
<td>2,289 (84.3%)</td>
<td>1.06 (0.66 - 1.70)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (9.3%)</td>
<td>98 (90.7%)</td>
<td>0.62 (0.29 - 1.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation at randomization</th>
<th>285 (19.4%)</th>
<th>1,187 (80.6%)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Active (amoxicillin and clavulanic acid)</td>
<td>167 (11.5%)</td>
<td>1,286 (88.5%)</td>
<td>0.59 (0.50 - 0.71)</td>
</tr>
</tbody>
</table>

| Received the trial intervention ‡ | 452 (15.5%) | 2,473 (84.5%) | Na     |

Note: P values corresponding to comparison by chi square test of association unless otherwise stated. The absolute numbers and percentage are shown. Univariable risk ratios of confirmed or suspected infection are also shown. RR (95CI%) – risk ratio (95% confidence interval). BMI - Body mass Index. Na – not applicable

* Mean (standard deviation) with comparison by t test

† Median (interquartile range) with comparison by Wilcoxon rank sum test.

‡ Women who did not receive the intervention were excluded from this analysis due to missing data on time of antibiotic administration.
Figures

Figure 1: Flow of participants

Figure 2: Risk of confirmed or suspected infection by perineal trauma subgroup

Figure 3a: Factors associated with confirmed or suspected infection in both trial arms combined (adjusted risk ratios)

Figure 3b: Factors associated with confirmed or suspected infection in the amoxicillin and clavulanic acid trial arm only (adjusted risk ratios)

Appendix Figure S1: Factors associated with confirmed or suspected infection in both trial arms combined: sensitivity analysis using multiple imputation of missing baseline information (adjusted risk ratios)
Figure 1: Flow of participants
Perineal trauma subgroup

<table>
<thead>
<tr>
<th></th>
<th>Co-amoxiclav</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No episiotomy or tear</td>
<td>249 (4.1%)</td>
<td>129 (3.4%)</td>
<td>1.18 (0.91, 1.52)</td>
<td>0.171</td>
</tr>
<tr>
<td>Tear only</td>
<td>2/133 (1.5%)</td>
<td>11/144 (7.6%)</td>
<td>2.09 (0.64, 6.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Episiotomy only</td>
<td>130/1102 (11.8%)</td>
<td>187/1091 (18.0%)</td>
<td>0.66 (0.53, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Episiotomy and tear</td>
<td>46/334 (13.8%)</td>
<td>107/392 (27.3%)</td>
<td>0.50 (0.37, 0.69)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>165/1619 (11.1%)</td>
<td>326/1605 (19.1%)</td>
<td>0.58 (0.46, 0.74)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: In the co-amoxiclav group, primary outcome data was missing for 5 women with either an episiotomy or tear. 9 women with a tear only, 65 women with an episiotomy only, and 17 women with an episiotomy and tear. In the placebo group, primary outcome data was missing for 7 women with neither an episiotomy or tear, 3 women with a tear only, 71 with episiotomy only and 21 with an episiotomy and tear.

There were no statistically significant differences between antibiotic and placebo groups in any of the subgroups no episiotomy or tear, tear alone or episiotomy alone. A very small number (5.2% of the total) had a cesarean section, with no statistically significant differences between antibiotic and placebo groups. Given the small number of cesarean sections, the difference in the frequency of cesarean section between the antibiotic and placebo groups (17.1% vs 16.4%) is not considered to be statistically significant and may represent a chance finding.