

Intravenous co-amoxiclav to prevent infection after operative vaginal delivery: the ANODE RCT

Marian Knight,^{1*} Virginia Chiocchia,¹
Christopher Partlett,¹ Oliver Rivero-Arias,¹
Xinyang Hua,¹ Ursula Bowler,¹ James Gray,²
Shan Gray,¹ Kim Hinshaw,^{3,4} Aethele Khunda,⁵
Philip Moore,² Linda Mottram,¹ Nelly Owino,¹
Dharmintra Pasupathy,⁶ Julia Sanders,^{7,8}
Abdul H Sultan,⁹ Raneer Thakar,⁹ Derek Tuffnell,¹⁰
Louise Linsell¹ and Edmund Juszczak¹ on behalf of the
ANODE Trial Collaborative Group

¹National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

²Department of Microbiology, Birmingham Women's & Children's NHS Foundation Trust, Birmingham, UK

³Department of Obstetrics and Gynaecology, City Hospitals Sunderland NHS Foundation Trust, Sunderland, UK

⁴Faculty of Health Sciences, University of Sunderland, Sunderland, UK

⁵Department of Women's Health, James Cook University Hospital, Middlesbrough, UK

⁶Department of Women and Children's Health, School of Life Course Sciences, King's College London, King's Health Partners, London, UK

⁷School of Healthcare Sciences, Cardiff University, Cardiff, UK

⁸Department of Women's Health, Cardiff and Vale University Health Board, Cardiff, UK

⁹Department of Obstetrics and Gynaecology, Croydon University Hospital, Croydon, UK

¹⁰Department of Women's Health, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK

*Corresponding author marian.knight@npeu.ox.ac.uk

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Scientific summary

The ANODE RCT

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Scientific summary

Background

Sepsis is a leading cause of direct and indirect maternal death in the UK; globally, it is estimated to cause almost 20,000 maternal deaths annually. In addition, for every maternal death in the UK there are an estimated 70 women who have severe sepsis (requiring level 2 or 3 critical care) but survive. An increased risk of sepsis following caesarean section has been recognised for many years, and the National Institute for Health and Care Excellence's guidance recommends the use of prophylactic antibiotics at all caesarean deliveries, based on substantial randomised controlled trial evidence of effectiveness. Previous National Institute for Health Research-funded studies have documented an additional risk associated with operative vaginal birth (forceps or ventouse/vacuum extraction), but a Cochrane review, updated in 2017, identified only one small previous trial of prophylactic antibiotics following operative vaginal birth. Given the small study size and extreme result, the review authors suggested that further robust evidence is needed.

In the light of this review, the Royal College of Obstetricians and Gynaecologists' guidance [Royal College of Obstetricians and Gynaecologists (RCOG). *Green-top Guideline Number 26: Operative Vaginal Delivery*. London: RCOG; 2011. URL: www.rcog.org.uk/globalassets/documents/guidelines/gtg_26.pdf (accessed 17 April 2018)] on operative vaginal delivery states that there are insufficient data to justify the use of prophylactic antibiotics in operative vaginal birth. Recognising the importance of antibiotic stewardship, the World Health Organization's recommendations on prevention and treatment of maternal peripartum infections explicitly state that routine antibiotic prophylaxis is not recommended for women undergoing operative vaginal birth, again citing a lack of evidence of benefit.

Twelve per cent of women in the UK undergo a forceps or ventouse birth, which is an estimated 90,000 women annually. The conservatively estimated incidence of maternal infection following operative vaginal birth is 4%, based on the one previous trial, resulting in an estimated 3600 women potentially having an infection after instrumental vaginal birth. Of these women, around 200 will be diagnosed with severe infection and up to four may die from their infection. There is, therefore, considerable scope for direct patient benefit from an effective preventative strategy.

Objective

The objectives were to investigate whether or not a single dose of prophylactic antibiotic following operative vaginal birth is clinically effective for preventing confirmed or presumed maternal infection and to determine the associated impact on health-care costs.

Methods

Trial design

The A randomised controlled trial of prophylactic ANTibiotics to investigate the prevention of infection following Operative vaginal DELivery (ANODE) trial was a multicentre, randomised, blinded, placebo-controlled trial conducted in the UK.

Setting

The trial was conducted in 27 consultant-led obstetric units in England and Wales.

Participants

Inclusion criteria

- Women aged ≥ 16 years who were willing and able to give informed consent.
- Women who had undergone an operative vaginal delivery at $\geq 36^{+0}$ weeks' gestation.

Exclusion criteria

Women were not eligible to enter the trial if *any* of the following applied:

- A clinical indication for *ongoing* antibiotic administration post delivery (e.g. because of a confirmed antenatal infection, third- or fourth-degree tears). Note that receiving antenatal antibiotics (e.g. for maternal group B streptococcal carriage or prolonged rupture of membranes) was not considered a reason for exclusion if there was no indication for ongoing antibiotic prescription post delivery.
- Known allergy to penicillin or to any of the components of co-amoxiclav, as documented in hospital notes.
- History of anaphylaxis (a severe hypersensitivity reaction) to another β -lactam agent (e.g. cephalosporin, carbapenem or monobactam), as documented in hospital notes.

Interventions

Women were randomised to receive either a single dose of intravenous co-amoxiclav (1 g of amoxicillin/200 mg of clavulanic acid) or a placebo (sterile saline).

Outcomes

Primary outcome

Confirmed or suspected maternal infection within 6 weeks of delivery, as defined by one of the following:

- a new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features or other systemic infection
- confirmed systemic infection on culture
- endometritis as defined by the US Centers for Disease Control and Prevention [Centers for Disease Control and Prevention (CDCP). *CDC/NHSN Surveillance Definitions for Specific Types of Infections*. Atlanta, GA: CDCP; 2013. URL: www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (accessed 15 November 2013)].

Secondary outcomes

Systemic sepsis

This was defined according to modified systemic inflammatory response syndrome criteria for pregnancy used in previous population-based surveillance studies.

Perineal wound infection

This was defined according to the Public Health England Surveillance definition of surgical site infection [Public Health England (Health Protection Agency). *Protocol for the Surveillance of Surgical Site Infection*. London: Public Health England; 2013. URL: http://webarchive.nationalarchives.gov.uk/1008070922242/http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947388966 (accessed 18 April 2019)].

Perineal pain/use of pain relief/dyspareunia/ability to sit comfortably to feed the baby/need for additional perineal care/breastfeeding

This was identified using standard questions developed for the Hands-On Or hands Poised (HOOP) (McCandlish R, Bowler U, van Asten H, Berridge G, Winter C, Sames L, *et al.* A randomised controlled trial of care of the perineum during second stage of normal labour. *Br J Obstet Gynaecol* 1998;**105**:1262–72) study and the Perineal REsuturing Versus expectant management following vaginal delivery complicated by a dehiscence Wound (PREVIEW) study (Dudley L, Kettle C, Thomas PW, Ismail KM. Perineal resuturing versus

expectant management following vaginal delivery complicated by a dehisced wound (PREVIEW): a pilot and feasibility randomised controlled trial. *BMJ Open* 2017;**7**:e012766).

Maternal general health

This was elicited by the EuroQol-5 Dimensions, five-level version.

Hospital bed stay/hospital and general practitioner visits/wound breakdown/antibiotic side effects

This was identified through specific questions included in the maternal questionnaire.

Statistics and analysis plan

Sample size

The single existing trial of antibiotic prophylaxis at operative vaginal birth found a 4% rate of postnatal infection, which was used as the estimate of the maternal infection rate following operative vaginal birth. To detect a 50% reduction, the reduction in infection rate seen in the antibiotic prophylaxis for caesarean section trials, with 90% statistical power at the two-sided 5% level of significance, required 1626 participants per group; with an estimated 5% loss to follow-up, the trial required 1712 participants per group, which was a total of 3424 women.

Statistical analyses

Statistical analyses were carried out according to a prespecified statistical analysis plan, finalised prior to unblinding. In summary, demographic and clinical data were summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables. Women were analysed in the groups to which they were randomly assigned, comparing the outcome of all women allocated to active treatment with all those allocated to the placebo arm, regardless of deviation from the protocol or treatment received (referred to as the intention-to-treat population). Binary outcomes were analysed using risk ratios, whereas continuous outcomes were analysed using either a mean or a median difference, as appropriate. As randomisation did not involve stratification or minimisation, the primary analysis was based on unadjusted estimates of effect. Two-sided statistical testing was performed throughout. A 5% level of statistical significance was used for analyses of the primary outcome, and 1% for secondary outcomes. The 95% confidence intervals are presented for analyses of the primary outcome and 99% confidence intervals are presented for secondary outcomes.

Sensitivity analyses

Four planned sensitivity analyses were carried out:

1. examining the primary outcome restricted to women who had not received antibiotics in the 7 days prior to giving birth, in case any masking of a prophylactic effect occurred by including of pre-treated women
2. examining the primary outcome excluding women prescribed antibiotics (other than the trial intervention) within 24 hours of giving birth, in case these women were already infected prior to administration of the intervention
3. a repeat analysis of the primary outcome restricted to women whose primary outcome was obtained based on data obtained between 6 and 10 weeks after women had given birth
4. a sensitivity analysis including centre as a random effect.

Results

Between March 2016 and June 2018, 3427 women were randomised, 1719 to the antibiotic arm and 1708 to the placebo arm. Seven women withdrew, leaving 1715 women in the antibiotic arm and 1705 in the placebo arm for inclusion in the intention-to-treat analysis. Primary outcome data and data on the

secondary outcome of perineal infection were available for 3225 out of 3420 women (94.3%), and data on the remaining secondary outcomes were available for 2593 women (75.8%). The intervention was administered a median of 3 hours after women had given birth.

Characteristics of participants were similar between the two trial arms. Women had a mean age of 30 years, approximately half were of normal body mass index and more than four-fifths were of white ethnicity. Overall, 77% of women were primiparous and 49% had labour induced. Sixty-five per cent of births were assisted by forceps and 35% by vacuum extraction. Eighty-eight per cent of women had an episiotomy, 31% had a perineal tear and > 99% had suturing of a perineal wound.

Primary outcome

The women randomised to the antibiotic arm of the trial were significantly less likely to have a confirmed or suspected infection within 6 weeks of giving birth than women randomised to the placebo arm [180/1619 (11.1%) vs. 306/1606 (19.1%); relative risk 0.58, 95% confidence interval 0.49 to 0.69]. The primary outcome was principally driven by one of the three components of the primary outcome: new prescription of antibiotics with specific indication. However, women randomised to the antibiotic arm were also significantly less likely to experience confirmed systemic infection on culture [11/1619 (0.6%) vs. 25/1606 (1.5%); relative risk 0.44, 95% confidence interval 0.22 to 0.89].

Secondary outcomes

The women randomised to the antibiotic arm of the trial were at significantly lower risk of most secondary outcomes than women randomised to placebo:

- a superficial perineal wound infection (75/1619 vs. 141/1606, respectively; relative risk 0.53, 99% confidence interval 0.37 to 0.76)
- a deep perineal wound infection (36/1619 vs. 77/1606, respectively; relative risk 0.46, 99% confidence interval 0.28 to 0.77)
- perineal pain (592/1296 vs. 707/1297, respectively relative risk 0.84, 99% confidence interval 0.76 to 0.93)
- use of pain relief for perineal pain (99/1296 vs. 138/1297, respectively; relative risk 0.72, 99% confidence interval 0.52 to 0.99)
- wound breakdown (142/1296 vs. 272/1297, respectively; relative risk 0.52, 99% confidence interval 0.41 to 0.67)
- need for additional perineal care (390/1296 vs. 543/1297, respectively; relative risk 0.72, 99% confidence interval 0.63 to 0.83)
- perineum ever too painful/uncomfortable to feed baby (136/1296 vs. 198/1297, respectively; relative risk 0.69, 99% confidence interval 0.53 to 0.90)
- any primary care or home visits in relation to perineum (361/1296 vs. 496/1297, respectively; relative risk 0.73, 99% confidence interval 0.63 to 0.84)
- any outpatient visits in relation to their perineum (95/1296 vs. 173/1297, respectively; relative risk 0.55, 99% confidence interval 0.40 to 0.75).

There were no significant differences in rates of:

- dyspareunia (299/544 vs. 280/514, respectively; relative risk 1.01, 99% confidence interval 0.87 to 1.17), noting that only 1058 women had resumed intercourse (41%)
- breastfeeding at 6 weeks (662/1296 vs. 657/1297, respectively; relative risk 1.01, 99% confidence interval 0.91 to 1.11)
- maternal hospital re-admission (63/1296 vs. 84/1297, respectively; relative risk 0.75, 99% confidence interval 0.49 to 1.14).

There were no differences between groups in hospital bed stay (median 1 day, interquartile range 1–2 days in each group; $p = 0.318$) or mean maternal health-related quality of life [EuroQol-5 Dimensions, five-level version, score mean 0.935 (standard deviation 0.098) in the antibiotic arm vs. 0.927 (standard deviation 0.111) in the placebo arm; $p = 0.048$].

Safety and adverse events

Only three women reported side effects of the intervention: two were in the antibiotic arm and one was in the placebo arm. The woman in the placebo arm reported a skin rash, and the women in the antibiotic arm reported other reactions (e.g. itching, swollen throat). There were no cases of anaphylaxis. Three serious adverse events were reported; only one, the itching reaction, was thought to be causally related to the intervention.

Discussion

The ANODE trial showed clear evidence of benefit of a single dose of intravenous co-amoxiclav administered to women a median of 3 hours after operative vaginal birth. Women in the antibiotic arm had a 42% reduction, from 19% to 11%, in the risk of suspected or confirmed infection. This was principally driven by the prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features, or other systemic infection, but women in the antibiotic arm also had a statistically significant (56%) reduction in the risk of confirmed systemic infection on culture, from 1.5% to 0.6%. Secondary outcomes also favoured the active (co-amoxiclav) arm, with significant reductions in rates of both deep and superficial perineal infection, perineal pain, wound breakdown, need for additional perineal care and general practitioner and outpatient visits in relation to perineal problems.

The single previous trial of antibiotic prophylaxis after operative vaginal birth reported on endometritis only, noting a rate of 4% in the no-antibiotic arm. This is considerably lower than the rate of suspected or confirmed infection that we observed in the ANODE trial (19% in the placebo arm) but, interestingly, using the strict Centers for Disease Control and Prevention surveillance definition, we observed a lower endometritis rate. The estimate of effect we observed for endometritis (relative risk 0.65, 95% confidence interval 0.34 to 1.24) in the ANODE trial is compatible with the effect estimate in the previous trial (relative risk 0.07, 95% confidence interval 0.00 to 1.17). Combining the results of the two trials using Mantel–Haenszel fixed-effect meta-analysis gives an overall relative risk 0.50 (95% confidence interval 0.27 to 0.93) for endometritis.

Although a single dose of co-amoxiclav almost halved the infection rate, 11% of women still had a confirmed or suspected infection after receiving antibiotic prophylaxis. The question therefore arises as to whether or not other interventions might reduce this further. We did not collect information about the aseptic techniques used at the time of operative vaginal birth; it is possible that further attention to aseptic technique at the time of birth may influence later outcomes. A Cochrane review (Fernandez R, Griffiths R. Water for wound cleansing. *Cochrane Database Syst Rev* 2012;**2**:CD003861) identified no difference in infection rates in surgical wounds cleansed with water versus other solutions (saline, procaine spirit) or no cleansing. The review identified only one small trial of wound-cleansing post episiotomy, which randomised 100 women to cleanse their episiotomy wounds with either water or procaine spirit; the authors report no difference in infection rates, but did not give exact figures. They note that women cleaned their wounds an average of five times per day and that all wounds were healed well by 14 days post partum. Therefore, there may be a place for further investigation of wound-cleansing after operative vaginal birth to see if infection rates are lower.

One in five women in the placebo arm and one in 10 in the antibiotic arm reported that they had experienced perineal wound breakdown. Although a previous feasibility study reported that most women whose perineal wound had dehisced had healed by 6–8 weeks, women described long-term impacts 6–9 months later, including psychosexual morbidity. It is probable, therefore, that the almost 50% reduction in wound breakdown reported in the antibiotic arm is associated with longer-term benefit to sexual function, even though we observed no difference in dyspareunia between the groups at 6 weeks post partum. Only 40% of women had resumed intercourse, which may also mask any potential beneficial effect of the active intervention.

In the light of current concerns over antimicrobial stewardship and the emergence of antimicrobial resistance, an assessment of the impact of the single prophylactic dose on overall antibiotic use is important. The additional economic evaluation conducted for the ANODE trial estimates that, for each additional 100 doses of antibiotic used in prophylaxis, 168 treatment doses will be saved, representing a 17% overall reduction in antibiotic use with a policy of universal prophylaxis.

Conclusion

Current national guidance on operative vaginal birth in the UK, the USA, Australia and New Zealand either do not mention or do not recommend antibiotic prophylaxis after instrumental vaginal birth. The World Health Organization's guidelines on prevention of maternal infection explicitly state that antibiotic prophylaxis is not recommended after instrumental vaginal birth on the basis of a lack of evidence of effectiveness. The ANODE trial has shown clear evidence of benefit of a single intravenous dose of prophylactic co-amoxiclav after operative vaginal birth; these results may lead to reconsideration of official policy/guidance. Further analysis of the mechanism of action of this single dose of antibiotic is needed to investigate whether or not earlier, pre-delivery or repeated administration could be more effective. Until these analyses are completed, there is no indication for administration of more than a single dose of prophylactic antibiotic, or for pre-delivery administration.

Trial registration

This trial is registered as ISRCTN11166984.

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