A randomized trial of prophylactic antibiotics for miscarriage surgery

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ORIGINAL ARTICLE

A Randomized Trial of Prophylactic Antibiotics for Miscarriage Surgery

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ABSTRACT

BACKGROUND

Surgical intervention is needed in some cases of spontaneous abortion to remove retained products of conception. Antibiotic prophylaxis may reduce the risk of pelvic infection, which is an important complication of this surgery, particularly in low-resource countries.

METHODS

We conducted a double-blind, placebo-controlled, randomized trial investigating whether antibiotic prophylaxis before surgery to complete a spontaneous abortion would reduce pelvic infection among women and adolescents in low-resource countries. We randomly assigned patients to a single preoperative dose of 400 mg of oral doxycycline and 400 mg of oral metronidazole or identical placebos. The primary outcome was pelvic infection within 14 days after surgery. Pelvic infection was defined by the presence of two or more of four clinical features (purulent vaginal discharge, pyrexia, uterine tenderness, and leukocytosis) or by the presence of one of these features and the clinically identified need to administer antibiotics. The definition of pelvic infection was changed before the unblinding of the data; the original strict definition was two or more of the clinical features, without reference to the administration of antibiotics.

RESULTS

We enrolled 3412 patients in Malawi, Pakistan, Tanzania, and Uganda. A total of 1705 patients were assigned to receive antibiotics and 1707 to receive placebo. The risk of pelvic infection was 4.1% (68 of 1676 pregnancies) in the antibiotics group and 5.3% (90 of 1684 pregnancies) in the placebo group (risk ratio, 0.77; 95% confidence interval [CI], 0.56 to 1.04; P=0.09). Pelvic infection according to original strict criteria was diagnosed in 1.5% (26 of 1700 pregnancies) and 2.6% (44 of 1704 pregnancies), respectively (risk ratio, 0.60; 95% CI, 0.37 to 0.96). There were no significant between-group differences in adverse events.

CONCLUSIONS

Antibiotic prophylaxis before miscarriage surgery did not result in a significantly lower risk of pelvic infection, as defined by pragmatic broad criteria, than placebo. (Funded by the Medical Research Council and others; AIMS Current Controlled Trials number, ISRCTN97143849.)

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Globally, 208 million women and adolescents become pregnant each year,[1] but 10 to 20% of pregnancies end in spontaneous abortion.[2] In many of these cases, surgery is needed to remove retained products of conception[3]; such surgery is one of the most common gynecologic operations performed worldwide. Infection is a serious potential consequence of surgery to complete a spontaneous abortion, in particular in low- and middle-income countries.[4] Pelvic infection can result in serious illness and death,[5] as well as long-term consequences from pelvic scarring, including increased rates of ectopic pregnancy and infertility.[6]

Antibiotic prophylaxis before some operations has been shown to reduce the risk of postoperative infections. A Cochrane review of 19 randomized, controlled trials of the use of antibiotic prophylaxis before uterine evacuation for induced termination of pregnancy showed that prophylactic antibiotics reduced pelvic infection for this specific indication.[7] However, for miscarriage surgery, evidence is lacking to show effectiveness,[8] with four small, single-center studies showing no significant benefit from prophylactic antibiotics. In addition to small size,[4,9-11] these studies had other methodologic limitations, including inadequate antibiotic dose[9] and poor adherence to the study protocol.[4]

International guidelines regarding antibiotic prophylaxis for surgery for incomplete spontaneous abortion are inconsistent. Some do not recommend antibiotics, reflecting the lack of evidence of efficacy,[12-14] whereas others acknowledge the lack of evidence but still advocate for their use on the basis of extrapolation of findings from other indications.[15]

The question of whether to use prophylactic antibiotics is particularly important in low- and middle-income countries. Rates of surgery for incomplete spontaneous abortion are high owing to low uptake of nonsurgical management approaches,[16] a higher incidence of infections after surgery in these countries than in high-income countries,[17-19] and poor access to resources to care for women in whom complications develop.[20] High-quality evidence is needed for rational antimicrobial prescribing.[21]

We designed this international, parallel-group, double-blind, placebo-controlled, randomized trial (Antibiotics in Miscarriage Surgery [AIMS]) to investigate whether, among women and adolescents undergoing surgery for incomplete spontaneous abortion, the use of presurgery prophylactic antibiotics (oral doxycycline, 400 mg, and oral metronidazole, 400 mg) would reduce the risk of pelvic infection. The trial was conducted in four countries: Malawi, Pakistan, Tanzania, and Uganda.

A Quick Take is available at NEJM.org

Methods

Trial Oversight

The AIMS trial was approved by ethical and regulatory bodies in each country and a United Kingdom ethics committee (reference number, LSTM13.15). Doxycycline and metronidazole were purchased from U.K. manufacturers, and the drugs were overencapsulated and packaged, alongside matched placebos, by Sharp Clinical Services UK. This company had no role in the design, conduct, analysis, or reporting of the trial.

Trial oversight was provided by an independent trial steering committee and an independent data and safety monitoring committee, whose members reviewed accruing safety data during the period of recruitment. The trial was registered before commencement, and the protocol was published previously[22] and is available with the full text of this article at NEJM.org. The first and last authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Trial Patients

Women and adolescents were recruited from hospitals in four countries: Malawi (three hospitals), Pakistan (five hospitals), Tanzania (three hospitals), and Uganda (two hospitals). Patients were eligible for inclusion if they had received a diagnosis of a spontaneous abortion at less than 22 weeks of gestation and were scheduled to undergo surgical evacuation of the uterus. Exclusion criteria were evidence of induced abortion, evidence of current pelvic infection, a need for immediate surgery, current or recent (within 7 days) antibiotic use, an age younger than 16 years, or other contraindication to doxycycline or metronidazole. A diagnosis of miscarriage was made by the clinician and confirmed on ultrasonography if indicated. Surgery was performed according to usual local practice.

Trial information was given in verbal and written formats in the local languages, and in-

structions regarding follow-up care were also provided in pictorial form. Written informed consent was provided by all patients before randomization and surgery.

TRIAL DESIGN AND DRUG REGIMEN

Patients were randomly assigned in a 1:1 ratio to receive either doxycycline (400 mg, taken orally as four tablets) and metronidazole (400 mg, taken orally as one tablet) or five matched placebos, taken approximately 2 hours before surgery. The appearance, route, and administration of the assigned intervention were identical in the antibiotic-prophylaxis group and the placebo group.

Computerized randomization was performed centrally through a secure Internet facility, with the use of minimization to balance trial-group assignments according to the patient's age (<35 or ≥35 years), gestational age (<12 weeks, ≥12 weeks, or unclear), type of miscarriage (incomplete or missed), and status with respect to human immunodeficiency virus (HIV) infection (known positive, known negative, or unknown). Patients, clinicians, and research staff were unaware of the trial-group assignments throughout the trial. Unblinding was permitted only in the event of a medical emergency.

OUTCOME MEASURES

The primary outcome was pelvic infection within 14 days after miscarriage surgery. Diagnosis required the presence of two or more of four clinical features — purulent yellow, green, or foul-smelling vaginal discharge; pyrexia (>38.0°C according to ear thermometry); uterine, parametrial, or adnexal tenderness on examination; and a white-cell count of more than 12×10^9 per liter — or the presence of one of the clinical features in addition to the clinician's judgment that antibiotics were needed for the treatment of pelvic infection.

At the start of the trial, pelvic infection was defined according to strict criteria, with diagnosis requiring two or more of the four clinical features above. These strict criteria are derived from Centers for Disease Control and Prevention (CDC) criteria and are consistent with current World Health Organization (WHO) guidelines.[12,23,24] However, during the conduct of the trial, it was observed by the examining clinicians that for some patients, only a single feature of infection was present, but the symptoms were of sufficient severity that the clinicians judged that there was pelvic infection and that treatment was required. There was concern that the original criteria, although highly specific, could lead to missed diagnoses in some patients with infection. This was potentially a patient safety issue, particularly where patient access to care was limited. Therefore, after discussion with the trial steering committee and the data and safety monitoring committee, it was decided that the diagnostic criteria by which pelvic infection was defined should be widened. The original strict definition of pelvic infection was reclassified as a secondary outcome. These changes were made before data were unblinded.

Other secondary outcomes were the components of the initial primary outcome, additional antibiotic use, additional analgesia (in addition to standard postoperative analgesia), unplanned hospital admissions, unplanned consultations, the duration of symptoms, and the number of days before the patient returned to usual activities. Adverse events included maternal death, diarrhea, vomiting, allergy, anaphylaxis, serious adverse events, and blood transfusion.

STATISTICAL ANALYSIS

The planned sample size of 3400 patients was estimated to provide 90% power to detect a relative between-group difference of 40% in the risk of pelvic infection (risk ratio, 0.60)[7] at a baseline risk of 7%, and 80% power at a baseline risk of 5%, under the assumption of a two-sided P value of 0.05 and a lack of ascertainment of the primary outcome in 10%. All binary outcomes are presented as risk ratios produced from a log-binomial regression model. Continuous measures were analyzed by means of linear regression and are presented as mean differences. All analyses were performed according to the intention-to-treat principle and adjusted for the minimization variables unless model convergence did not occur, in which case unadjusted estimates were produced. Sensitivity analyses for the primary outcome include an unadjusted analysis, a per-protocol analysis, and assessment of missing primary outcome data, under the assumption that all missing outcomes were pelvic infections and by means of a multiple-imputation approach.

Eight prespecified subgroup analyses were performed on the basis of maternal age (<35 or

≥35 years), gestational age (<12 weeks, ≥12 weeks, or unclear), status with respect to HIV infection (known positive, known negative, or unknown), miscarriage type (incomplete or missed), timing of antibiotic administration (<2 hours, 2 to 4 hours, or >4 hours before surgery), country (Malawi, Pakistan, Tanzania, or Uganda), patient residence (urban or rural), and type of miscarriage surgery (manual vacuum aspiration, suction curettage, or sharp curettage). These analyses were limited to the primary outcome only. The treatment effect within these subgroups was examined by the addition of the treatment-by-subgroup interaction measurement to the log-binomial regression model.

The analysis plan did not include correction for multiple comparisons when we conducted tests for secondary outcomes or subgroup analysis. Results are therefore reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects within subgroups or for secondary outcomes. All analyses were generated with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

The trial-group assignments, loss to follow-up, and reasons for withdrawal are summarized in Figure 1. Of the 4098 women and adolescents who were assessed for eligibility, 3412 underwent randomization from June 2014 through April 2017. A total of 1705 patients were assigned to antibiotic prophylaxis and 1707 to placebo. After withdrawals, 1700 patients in the antibiotic-prophylaxis group and 1704 in the placebo group were included in the intention-to-treat analysis, with primary outcome data obtained on 3360 (98.7%) of these patients.

The baseline characteristics were similar in the antibiotic-prophylaxis group and the placebo group (Table 1; and Table S1 in the Supplementary Appendix, available at NEJM.org). A majority of the patients were educated to primary school level, obtained water from a shared tap or pump, and used a nonventilated pit latrine. Sharp curettage was used for the surgical procedure in 70.0% of the patients, syringe-based suction (manual vacuum aspiration) in 23.2%, and suction curettage in 6.2%; the remaining 0.6% of the patients did not undergo surgery.

PRIMARY OUTCOME

The rate of pelvic infection was 4.1% in the antibiotic group (68 of 1676 pregnancies), as compared with 5.3% (90 of 1684 pregnancies) in the placebo group (risk ratio, 0.77; 95% confidence interval [CI], 0.56 to 1.04; P=0.09) (Table 2). The point estimates from prespecified sensitivity analyses were consistent with the point estimate from the primary analysis (Table S2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The rate of pelvic infection that was diagnosed according to the original strict definition was 1.5% (26 of 1700 pregnancies) in the antibiotic-prophylaxis group, as compared with 2.6% (44 of 1704 pregnancies) in the placebo group (risk ratio, 0.60; 95% CI, 0.37 to 0.96). Fewer patients in the antibiotic-prophylaxis group than in the placebo group received additional analgesia (risk ratio, 0.72; 95% CI, 0.57 to 0.92) or had an unplanned consultation (risk ratio, 0.60; 95% CI, 0.37 to 0.97). Other prespecified secondary outcomes, such as duration of pain or bleeding, did not differ substantially between the two groups (Table 2).

SUBGROUP ANALYSES

There were no significant interactions according to maternal age, gestational age at surgery, presence or absence of HIV infection, type of miscarriage, country of recruitment, time between administration of the trial intervention and the start of surgery, or residence in an urban or rural location (Table S3 in the Supplementary Appendix). The only significant interaction suggesting a subgroup effect was for type of surgery (P=0.02 for interaction). The effect of prophylactic antibiotics on the risk of pelvic infection appeared greater in patients who underwent manual vacuum aspiration (rate of infection, 1.3% in the antibiotic-prophylaxis group and 4.1% in the placebo group; risk ratio, 0.32; 95% CI, 0.12 to 0.86) than in those who underwent sharp curettage (rate of infection, 5.3% in the antibiotic-prophylaxis group and 6.0% in the placebo group; risk ratio, 0.89; 95% CI, 0.64 to 1.23); however, there was no correction made for the multiple comparisons.

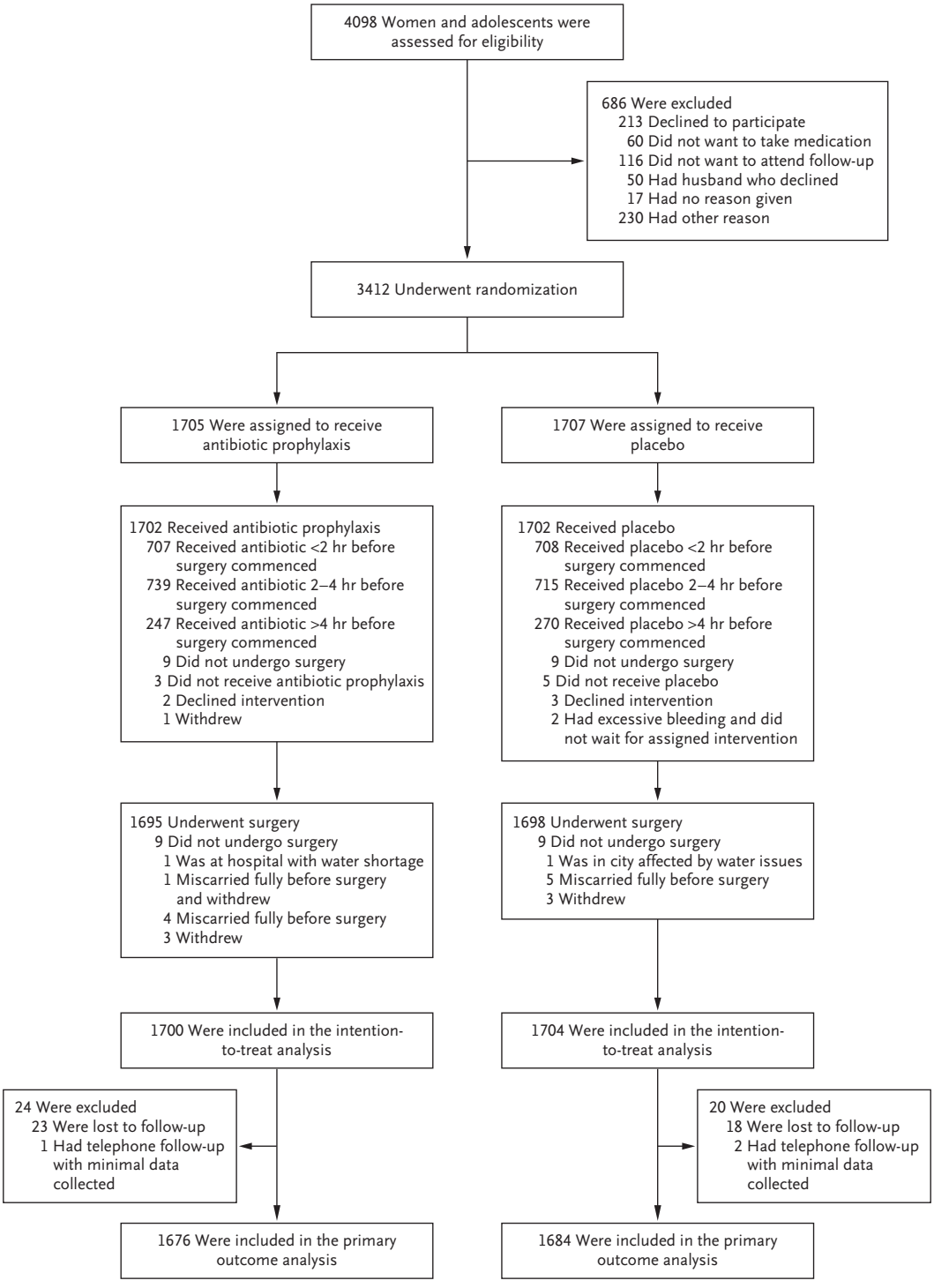

Figure 1. Enrollment, Randomization, Follow-up, and Outcomes.

Five patients who were assigned to receive antibiotic prophylaxis were not included in the intention-to-treat analysis: one who withdrew before receiving antibiotic prophylaxis, one who miscarried fully before surgery and then withdrew, and three who withdrew and did not undergo surgery. Three patients who were assigned to receive placebo were not included in the intention-to-treat analysis, all of whom withdrew and did not undergo surgery.

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Antibiotic Prophylaxis (N=1705)	Placebo (N=1707)
Age†		
Distribution — no. (%)		
<35 yr	1500 (88.0)	1505 (88.2)
≥35 yr	205 (12.0)	202 (11.8)
Mean — yr	26.2±6.6	26.0±6.6
Gestational age — no. (%)†		
<12 wk	838 (49.1)	835 (48.9)
≥12 wk	866 (50.8)	871 (51.0)
Unclear	1 (0.1)	1 (0.1)
Type of miscarriage — no. (%)†		
Incomplete	1429 (83.8)	1429 (83.7)
Missed	276 (16.2)	278 (16.3)
HIV status — no. (%)†		
Known positive	33 (1.9)	34 (2.0)
Known negative	935 (54.8)	945 (55.4)
Unknown	737 (43.2)	728 (42.6)
Country — no. (%)		
Malawi	1071 (62.8)	1074 (62.9)
Pakistan	177 (10.4)	176 (10.3)
Tanzania	110 (6.5)	100 (5.9)
Uganda	347 (20.4)	357 (20.9)
Time between administration of trial intervention and start of surgery		
No. of patients evaluated	1693	1693
Median (IQR) — hr	2.2 (1.6–3.2)	2.2 (1.5–3.3)
Current residence — no. (%)		
Rural	547 (32.1)	513 (30.1)
Urban	1158 (67.9)	1194 (69.9)
Type of surgery — no. (%)		
Manual vacuum aspiration	394 (23.1)	397 (23.3)
Suction curettage	103 (6.0)	109 (6.4)
Sharp curettage	1198 (70.3)	1192 (69.8)
No surgery	10 (0.6)	9 (0.5)
Education — no. (%)		
No formal education	67 (3.9)	48 (2.8)
Did not complete primary education	453 (26.6)	476 (27.9)
Completed primary education	589 (34.5)	618 (36.2)
Completed secondary education	370 (21.7)	346 (20.3)
Completed tertiary education	226 (13.3)	219 (12.8)
Latrine — no. (%)		
No latrine	19 (1.1)	8 (0.5)
Nonventilated pit latrine	1191 (69.9)	1246 (73.0)
Ventilated improved pit latrine	181 (10.6)	178 (10.4)
Flush toilet	314 (18.4)	275 (16.1)
Water to wash in — no. (%)		
Piped and tapped water	398 (23.3)	374 (21.9)
Shared tap or pump	1252 (73.4)	1269 (74.3)
Open water well	53 (3.1)	59 (3.5)
River, pond, or lake	2 (0.1)	5 (0.3)

* Plus–minus values are means ±SD. There were no significant differences between the trial groups in any characteristic, except type of latrine (P=0.04). Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Shown are minimization variables.

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Antibiotic Prophylaxis	Placebo	Risk Ratio or Difference in Means (95% CI)†
Primary outcome: pelvic infection defined by pragmatic broad criteria — no./total no. (%)‡	68/1676 (4.1)	90/1684 (5.3)	0.77 (0.56 to 1.04)§
≥2 Clinical features and antibiotics used to treat infection	24/1676 (1.4)	41/1684 (2.4)	
≥2 Clinical features and no antibiotics used to treat infection	2/1676 (0.1)	3/1684 (0.2)	
1 Clinical feature and need for antibiotics per clinician judgment	42/1676 (2.5)	46/1684 (2.7)	
Secondary outcomes			
Pelvic infection defined by strict criteria — no./total no. (%)¶	26/1700 (1.5)	44/1704 (2.6)	0.60 (0.37 to 0.96)
Additional antibiotic use — no./total no. (%)	131/1676 (7.8)	164/1684 (9.7)	0.81 (0.65 to 1.01)
Additional analgesia — no./total no. (%)	106/1676 (6.3)	147/1684 (8.7)	0.72 (0.57 to 0.92)
Unplanned ward admission — no./total no. (%)	15/1676 (0.9)	21/1684 (1.2)	0.72 (0.37 to 1.39)
Unplanned consultation — no./total no. (%)	25/1700 (1.5)	42/1704 (2.5)	0.60 (0.37 to 0.97)
Abdominal or pelvic pain			
Presence of abdominal or pelvic pain — no./total no. (%)‖	210/1700 (12.4)	260/1704 (15.3)	0.80 (0.68 to 0.95)
Duration of abdominal or pelvic pain — days	2.9±3.0	2.6±2.8	0.3 (−0.2 to 0.8)
Vaginal bleeding			
Presence of vaginal bleeding — no./total no. (%)‖	448/1700 (26.4)	451/1704 (26.5)	1.00 (0.93 to 1.07)
Duration of vaginal bleeding — days	1.8±2.5	1.6±1.8	0.2 (−0.1 to 0.5)
Delay to usual activities			
Occurrence of delay to usual activities — no./total no. (%)‖	7/1671 (0.4)	10/1678 (0.6)	0.70 (0.27 to 1.84)
Duration of delay to usual activities — days	14.3±13.8	8.3±4.3	5.7 (−6.3 to 17.8)

* Plus–minus values are means ±SD.
† Risk ratios are presented for binary outcomes; values of less than 1 favor antibiotic prophylaxis. Differences in means are presented for duration outcomes; values of less than 0 favor antibiotic prophylaxis. All estimates were adjusted for minimization variables when possible. Because the widths of the confidence intervals were not adjusted for multiple comparisons, they should not be used to infer definitive treatment differences.
‡ For the primary outcome analysis, pelvic infection was defined by the presence of two or more of four clinical features (purulent vaginal discharge, pyrexia, uterine tenderness, and leukocytosis) or by the presence of one of these features and the clinically identified need to administer antibiotics.
§ P=0.09. P values were not calculated for secondary outcomes.
¶ For the secondary outcome analysis, pelvic infection was defined by the presence of two or more of four clinical features: purulent vaginal discharge, pyrexia, uterine tenderness, and leukocytosis. Shown are the patients included in the intention-to-treat analysis.
‖ These outcomes were not prespecified.

ADVERSE EVENTS

There were no significant differences in the rates of diarrhea, vomiting, or blood transfusion between the antibiotic-prophylaxis group and the placebo group (Table 3). There were no cases of anaphylaxis reported and a single case of allergy in the antibiotic-prophylaxis group. One patient in the placebo group died 2 days after randomization and miscarriage surgery, subsequent to the surgical complication of uterine perforation with associated bowel injury. Serious adverse events were uncommon (16 [0.9%] in the antibiotic-prophylaxis group and 25 [1.5%] in the placebo group), and the incidence of such events did not differ significantly between the two groups.

DISCUSSION

In this large, multicountry, multicenter, placebo-controlled, randomized trial, we found that the use of prophylactic antibiotics before miscarriage surgery did not result in a significantly lower risk of pelvic infection than the use of placebo, when pelvic infection was defined pragmatically to incorporate clinicians' judgment. In a secondary analysis that used strict criteria to define pelvic

Table 3. Adverse Events.

Adverse Event	Antibiotic Prophylaxis	Placebo	Risk Ratio (95% CI)*	P Value
Serious adverse event — no./total no. (%)†	16/1705 (0.9)	25/1707 (1.5)	0.64 (0.34–1.20)	0.16
Cause of serious adverse event — no.‡				
Heavy bleeding	2	5		
Bacterial meningitis and cerebral abscess	1	0		
Ectopic pregnancy	3	2		
Hysterectomy for myometritis	0	1		
Hysterectomy for tubo-ovarian abscess	1	0		
Malaria	3	1		
Pneumonia	0	1		
Retained products of conception	6	12		
Severe vomiting	0	1		
Uterine perforation	0	2		
Diarrhea — no./total no. (%)	21/1700 (1.2)	23/1704 (1.3)	0.92 (0.51–1.65)	0.77
Vomiting — no./total no. (%)	18/1700 (1.1)	15/1704 (0.9)	1.20 (0.61–2.38)	0.59
Allergy — no./total no. (%)	1/1700 (0.1)	0/1704	—	—
Anaphylaxis — no./total no. (%)	0/1700	0/1704	—	—
Death — no./total no. (%)	0/1677	1/1686 (0.1)	—	—
Blood transfusion — no./total no. (%)	1/1677 (0.1)	4/1686 (0.2)	0.25 (0.03–2.25)	0.17

* Risk ratios of less than 1 favor antibiotic prophylaxis. All values were adjusted for minimization variables when possible.
† An adverse event was classified as a serious adverse event if it resulted in death, was life-threatening, resulted in hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, or consisted of a congenital anomaly or birth defect.
‡ Causes of serious adverse events were not prespecified outcomes.

infection, based on the CDC definition,[23] we found that patients who received prophylactic antibiotics had a lower rate of pelvic infection than those who received placebo, but we did not adjust for multiple comparisons of secondary outcomes.

We chose the antibiotics used in this trial after careful consideration. In addition to their demonstrated effectiveness in treating pelvic infection, doxycycline and metronidazole are widely available internationally; both are included on the WHO model list of essential medicines[25] and are inexpensive and heat-stable. The oral route simplifies use, and administration of a single dose reduces issues of adherence that were identified previously,[4] with doxycycline being particularly well suited to this approach owing to its long half-life. Allergy to either doxycycline or metronidazole is very uncommon, which is vital if they are to be used widely for prophylaxis in resource-limited settings. No serious adverse reactions to these medications were reported in our trial. There was concern that the use of doxycycline at a high dose before surgery might increase nausea and vomiting, but we found a similar frequency of these symptoms as well as other adverse effects in the active-treatment group and the placebo group.

At the start of the trial, we defined pelvic infection using strict criteria based on CDC guidance,[23] WHO guidance,[12] a review of outcomes in existing trials of pelvic infection, and consensus among the international investigator group. Diagnosis according to these strict criteria has been common in the existing literature and is considered meaningful from the perspectives of patients and policy makers. However, we widened the criteria that we used for diagnosis during the course of the trial, well before the unblinding of the data, in response to safety

concerns of some trial clinicians that some pelvic infections were being missed when the strict criteria were used. Whereas inclusion of clinician judgment among the criteria for diagnosis would be expected to improve the sensitivity for identifying pelvic infection, it is also likely to have decreased specificity; it can be challenging to distinguish clinical findings that are part of the normal postoperative period or noninfective surgical complications from those indicating pelvic infection. The addition of clinician judgment to the pragmatic definition is likely to have diluted the observed treatment effect, with the change in criteria adding 42 events to the antibiotic-prophylaxis group and 46 events to the placebo group.

There has been little evidence to guide clinical practice,[8] with the existing trials evaluating antibiotic prophylaxis in patients undergoing miscarriage surgery limited by size and quality.[4,9-11] We identified four trials (involving a total of 869 participants) of prophylactic antibiotic use in women undergoing surgery for miscarriage; these were all conducted at single centers and used different antibiotics and assessed different outcomes. None of the four studies showed a significant benefit, although they were not sufficiently powered to identify an important difference.

In conclusion, in this multicountry, multicenter, double-blind, placebo-controlled, randomized trial conducted in low- and middle-income countries, we found that antibiotic prophylaxis with doxycycline and metronidazole before miscarriage surgery did not result in a significantly lower 14-day risk of pelvic infection, as defined by pragmatic broad criteria, than placebo. However, results suggested a possible benefit when pelvic infection was defined by strict criteria.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article is dedicated to the memory of Dr. Godfrey Mbaruku and his inspiring, lifelong service to global maternal health.

APPENDIX

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