Early clindamycin for bacterial vaginosis in pregnancy (premeva): a multicentre, double-blind, randomised controlled trial

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Early Clindamycin for Bacterial Vaginosis in Low-Risk Pregnancy

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Abstract

Background

Treatment for bacterial vaginosis in pregnant women to reduce risk of spontaneous very preterm birth and late miscarriage remains controversial. We conducted a randomized control trial to determine whether bacterial vaginosis treatment could decrease spontaneous very preterm births and late miscarriages.

Methods

The PREMEVA trial was a multicenter randomized control double-blinded trial performed in 40 French centers. A total of 84,530 pregnant women were screened for bacterial vaginosis before 14 weeks of gestation. Women with bacterial vaginosis in the first trimester of pregnancy were randomly assigned to three similarly sized parallel arms: one four-day course of 600 mg oral clindamycin daily, three four-day courses of 600 mg daily a month apart or placebo. The primary outcome was a composite of late miscarriage (16-21 weeks) or spontaneous very preterm delivery (22-32 weeks) according to clindamycin treatment or placebo. Secondary outcomes included spontaneous preterm delivery before 37 weeks (22-36 weeks).

Findings

Between 04/01/2006 and 06/30/2011, 84,530 pregnant women were screened before 14 weeks of gestation, 5630 (6·7%) had bacterial vaginosis and 2869 were randomized. The primary outcome did not differ significantly between the groups (1·2% in the clindamycin group and 1.0% in the placebo group, relative risk, 1.10; 95% confidence interval [CI], 0·53 to 2·32), nor in the rate of spontaneous preterm delivery before 37 weeks (4·8% and 4·1%, respectively; relative risk, 1·17; 95% CI, 0·81 to 1·69). Side effects were more common in the clindamycin group (3·0% *vs* 1·3%, p=0·003) but not severe.

Interpretation

Systematic screening and subsequent treatment for bacterial vaginosis in low-risk pregnant women does not decrease late miscarriage, spontaneous very preterm birth, or spontaneous preterm birth.

Funding

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Introduction

Preterm birth is the leading cause of perinatal mortality and morbidity worldwide [1,2]. Preterm is defined as child born alive before 37 weeks of pregnancy are completed. Seventy percent of preterm births occur in women that had no past history of preterm birth [3,4].

Preterm birth can be individualized into sub-groups based on gestational age: extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks). Extremely preterm and very preterm birth lead to a high rate of neurological and respiratory complications in newborn [2].

While, preterm births are multifactorial such as tobacco or ethnic origin, several clinical studies show also an association between preterm birth and bacterial vaginosis [5-7]. Bacterial vaginosis consists in an excessive growth of certain vaginal bacteria leading to a major imbalance of the vaginal microbiota characterized by a decreased abundance of Lactobacillus species and an increased abundance of anaerobic species and genital mycoplasmas. Bacterial vaginosis can be diagnosed either clinically using the Amsel criteria [8] (i.e.: presence of clue cells, a vaginal pH greater than 4·5, profuse white discharge, and a fishy odor when the vaginal discharge is exposed to potassium hydroxide) or in the laboratory using the Nugent score [10]. The Nugent score consists in establishing the decrease in *Lactobacillus* species and increase in anaerobic species on Gram-stained vaginal smear. It has been shown that the Nugent score is a more reproducible marker than the Amsel criteria in a clinical study [9]. The prevalence of bacterial vaginosis differs between different regions worldwide. In our region, bacterial vaginosis prevalence was estimated at 7.1% (95% CI: 6.6–7.5%) in a cohort of 14,193 pregnant women by the Nugent score.

During pregnancy, the occurrence of bacterial vaginosis is associated with preterm birth (odds ratio 2·16) 11. However, the pathophysiological mechanism through which bacterial vaginosis affects ongoing pregnancy remains unclear. Bacterial dysbiosis occurring during bacterial vaginosis may lead to vaginal infection that could ascend into the uterus before and early during pregnancy [12]. Therefore, several authors hypothesize that the early antibiotic treatment of bacterial vaginosis during pregnancy might prevent some preterm births.

Since the 1990s, several antibiotic regimens have been studied in pregnant women with bacterial vaginosis in randomized-controlled trials. Two recent meta-analyses are contradictory [13,14]. The first concluded that clindamycin prescribed before 22 weeks of gestation might reduce the risk of preterm birth by 40% [13], while the second found no

reduction at all, even when antibiotics were initiated before 20 weeks [14]. However, both meta-analyses recommend reassessing early treatment of bacterial vaginosis within the first trimester of pregnancy in larger cohorts [13,14].

The PREMEVA project (Prevention of Very PREterM Delivery by Testing for and Treatment of Bacterial VAginosis) is a randomized controlled trial to test the effectiveness of early clindamycin to reduce the rate of births before 32 weeks in low-risk pregnant women with bacterial vaginosis during the first trimester.

Methods

Study design and participants

The regional institutional review board approved the study (Comité de Protection des Personnes participant à la Recherche Biomédicale - PHRC2004/1918 PROM04-06-859). Between 2006 and 2011, all pregnant women in the Nord-Pas de Calais region of France were offered free screening for bacterial vaginosis during their first trimester of pregnancy on self-taken vaginal samples [15]. Bacterial vaginosis was defined by a Nugent score of 7 or higher on these samples. Women with bacterial vaginosis who had no prior history of either late miscarriage (from 16 to 21 weeks, 6 days) or preterm birth (from 22 to 36 weeks, 6 days) were asked to participate in a randomized multicenter placebo-controlled double-blind trial with three similarly-sized parallel groups: a four-day course of 300 mg oral clindamycin twice daily, three four-day courses of 300 mg twice daily spaced one month apart, or placebo.

The inclusion criteria were gestational age less than 15 weeks, a maternal age of 18 years or older, and the ability to speak French and provide written informed consent. The exclusion criteria were known allergy to clindamycin, vaginal bleeding within the week prior to proposed screening of bacterial vaginosis, or plans to give birth in a different region. Women with a history of late miscarriage (from 16 to 21 weeks 6 days) or preterm delivery (from 22 to 36 weeks, 6 days) were also excluded, but offered to participate in another trial ("high risk" trial).

Randomization and masking

All participants provided written informed consent before enrollment. Physicians in each center included women in each of the 40 study centers. Women were randomized by a computer-generated random allocation sequence (T4trials/T4fields©, Paris, France) and received a numbered box corresponding to their randomization sequence. Each box contained three blister packs numbered from 1 to 3, each containing 8 capsules of study drug or placebo. The regimen was one capsule to be taken orally morning and evening for 4 days, once a month for three months. There were three different types of boxes, depending on the group. Study participants and all healthcare professionals were blinded to the composition of the boxes: one third had contained exclusively 300-mg clindamycin capsules; one third contained 300-mg clindamycin capsules in blister pack n°1 and placebo in the other two blister packs; and the remaining third contained placebo capsules in all three blister packs. The clindamycin and placebo capsules were manufactured specifically for the study and were strictly identical

in appearance (LC2 Pharma©, Lentilly, France). Randomization was stratified by center and in blocks of six. The randomization list was held by the study kit manufacturer. Women were instructed to begin treatment the day after randomization and use the blister packs in their numbered order. Use of other treatments, including antibiotics was permitted during the study period. Nugent score was not reassessed during pregnancy.

Procedures

Each woman performed in screening center a vaginal self-sample with one swab to performed immediately the Nugent score. Vaginal secretions were spread on a clean microscopy slide and heat-fixed within 4 h. The vaginal smear was then Gram-stained. Examining several microscopic fields at a 10-fold magnification assessed bacterial and cellular abundance. Nugent score was established as described elsewhere [9]. Scores of 0–3 were considered normal (*lactobacillus*-dominant), 4–6 were labeled as intermediate (mixed morphotypes), and 7–10 were indicative of bacterial vaginosis (absence of *lactobacilli* and predominance of the other two morphotypes). To standardize the reading of the Nugent test before the study began, all technicians in each participating clinical laboratory received a training video, a technical brochure, and training slides. Three independent clinical pathologists reread the initial slides of the study. During the study period, they selected 4 slides from each laboratory (1 with an unreadable slide for which no Nugent score could be determined, and three including one with a score between 0 and 3, 4 and 6, and 7 and 10). Concordances were evaluated by calculating Cohen's Kappa coefficient.

Outcomes

The primary outcome was the onset of late miscarriage or spontaneous very preterm birth defined in our study as between 16 and 32 weeks, 6 days. Preterm deliveries were considered spontaneous if they followed the spontaneous onset of labor and/or premature rupture of the membranes (PROM), regardless of final mode of delivery.

The secondary outcomes were spontaneous preterm delivery (22 to 36 weeks, 6 days), PROM, and any of the following either before or at term: abruptio placentae, signs of prenatal chorioamnionitis, maternal fever ≥ 38°C during labor or for more than 24 hours postpartum, and post-partum wound infection. Fetal and neonatal outcomes considered were in utero death after 22 weeks, signs of suspected or confirmed neonatal infection, admission to the neonatal intensive care unit, and perinatal death (defined by either in utero death or neonatal death up to one month after birth). Serious neonatal morbidity was defined by bronchopulmonary

dysplasia (oxygen therapy at 36 weeks of life), or severe cerebral lesions on ultrasound scan defined as grade III - IV hemorrhages as recorded by Papile and colleagues [16] or periventricular leukomalacia grade I-III as recorded by de Vries and colleagues [17]. Poor perinatal outcome was defined by serious neonatal morbidity or perinatal death.

Statistical analysis

The outcomes were compared between the placebo group and the two clindamycin groups combined. Additionally, the two groups receiving clindamycin were compared in a planned supplemental analysis to determine the efficacy of repeated versus single courses of clindamycin. No interim analyses were planned. Because the percentage of preterm deliveries before 32 weeks and of late miscarriages from 16-21 weeks is estimated at approximately 2% in France [18] and this risk is reported as doubled in women with bacterial vaginosis [11], we expected a rate of late miscarriages and preterm deliveries of approximately 4% in the placebo group. As a reduction of 50% was expected with antibiotic treatment [13,19], the sample-size was calculated to be able to identify a reduction in the incidence of late miscarriage or spontaneous preterm delivery from 4% in the placebo group to 2% in the combined clindamycin group. To detect this difference with a power of 80% and a two-sided type I error, we needed to recruit 900 patients in the placebo group and 1800 in the clindamycin groups combined. With the frequency of bacterial vaginosis estimated at 5 to 10%, we needed to screen at least 80,000 women. The trial took place in a region of around 4 million inhabitants, where approximately 58,000 children are born each year, 6·9% of them preterm [20].

Participant data were collected at inclusion and after delivery. To verify the spontaneous or induced nature of deliveries, each pregnancy outcome before 37 weeks was systematically reviewed by four study investigators; two obstetricians and two midwives all blinded to treatment allocation. An independent data safety committee monitored the trial. The database was frozen in April 2013, before unblinding. Data from all participants were independently analyzed according to the arm to which they were randomly assigned, regardless of whether they took the study treatment or not (intention-to-treat). A per-protocol analysis was also performed to verify that exclusion of patients incorrectly included in the study and of those who failed to adhere to the protocol did not modify the conclusions. Categorical variables were compared with the chi-square test, and continuous variables with Student's t-test. The percentages are reported in parentheses, and means are reported with the standard deviation of

the distribution. P values of less than 0·05 were considered to indicate statistical significance. The relative risks are reported with their 95% confidence intervals.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Vaginal sample smears from 84,530 women were read to determine Nugent scores. From years 2006 to 2011, screening involved approximately 10, 18, 26, 36, 40 and 44% of women who delivered in our region of France (mean 28%). After lab technicians were trained for the Nugent test, the diagnostic agreement for the initial smears was very satisfactory (2870 smears, Kappa=0·87) (supplemental data). Quality control during the study period showed equally good agreement (149 clinical laboratories, 596 smears, Kappa= 0·81) (supplemental data). Figure 1 shows the enrollment and follow-up of the women who participated in the trial. Of the 5630 women (6·7%) eligible for the study (Nugent score ≥7), 2402 did not undergo randomization for various reasons and 359 met exclusion criteria. The remaining 2869 were included and randomly assigned to receive clindamycin (n=1911: 943 to one course and 968 to three) or placebo (n= 958). A total of 7 women in the clindamycin group and 2 in the placebo group were lost to follow-up. The last women included in the trial gave birth on February 1, 2012.

Table 1 summarizes baseline characteristics according to study group. These characteristics were not significantly different between the two groups, except that more women smoked in the clindamycin group (35 vs 30%, p=0·007). Median gestational age at randomization was 12 weeks, 6 days (interquartile range [11 weeks, 1 day to 13 weeks, 6 days]). Half the women were nulliparous. There were 53 multiple pregnancies, including 5 sets of triplets. Finally, the incidence of Nugent scores greater or equal to 9 was not significantly different between groups.

Side effects were reported by 3·0% and 1·3%, respectively (p=0·003) (Table 2). The most common side effect was diarrhea (1·6% in the clindamycin group, 0·4% in the placebo group, p=0·007), but abdominal pain was also observed in the clindamycin group. Neither group reported a severe side effect or adverse event. The percentage of women who stopped taking the study treatment was higher in the clindamycin than the placebo group (19·6% compared with 16·3%, p=0·03).

For the course of pregnancy, bleeding in the second and third trimesters, threatened preterm labor, prenatal signs of chorioamnionitis, and premature rupture of the membranes were not significantly different between clindamycin and placebo groups.

As less than 50% of women gave their treatment box back at the end of pregnancy, it was impossible to evaluate treatment compliance by counting remaining capsules. During the trial,

we decided to contact by phone at least 5% of consecutive women included of the study at the beginning of their third trimester. Over a 38-day period, 247 consecutive women were contacted, accounting for just over 8% of the 2869 women included in the study. Eight had had spontaneous miscarriages during the first trimester (3·2%). Of the 239 others, we could not reach 12 (5·0%) and 40 had taken less than two-thirds of the capsules or did not remember how many they had taken, or hadn't taken any (16·7%). Finally, 187 had taken at least two-thirds of the 24 capsules, therefore the estimated compliance was 78·2%; 95% CI 72·5 to 83·3%.

The incidence of the primary outcome — late miscarriage or spontaneous very preterm delivery (16 weeks to 32 weeks, 6 days) — was 1·2% in the clindamycin group and 1·0% in the placebo group (p=0·82) (table 3). Planned analyses showed that neither component of the primary outcome differed significantly between the two groups, nor did any of the secondary outcomes. The groups had similar rates of spontaneous preterm delivery (22 weeks to 36 weeks, 6 days, (4·8% in the clindamycin and 4·1% in the placebo groups) and total preterm delivery (6·7% and 5·8%, respectively). These results did not show that clindamycin was associated with a reduction of preterm labor, prenatal chorioamnionitis, PPROM or PROM or postpartum fever (tables 2 and 3).

Adverse fetal and neonatal outcomes also did not differ significantly between the clindamycin and placebo groups (table 4). They did not differ for either neonatal weight < 1500 g (1·3 vs 0·6%, respectively, p=0·10), neonatal weight < 2500 g (8·5 vs 8·0%, p=0·62), neonatal sepsis, admission to the neonatal care unit, perinatal death, neonatal mortality or morbidity, or the frequency of unfavorable perinatal outcomes (1·1 vs 1·2%, respectively, p=0·91). Per-protocol analyses did not change these results, nor did the supplemental analysis comparing the single course to the multiple course of clindamycin.

Discussion

Our study showed that treatment by oral clindamycin in women at low risk of preterm birth with bacterial vaginosis during the first trimester of pregnancy did not reduce the risk of late miscarriage or of spontaneous very preterm or preterm delivery.

Clindamycin is one of the two most often used antibiotics to treat bacterial vaginosis during pregnancy [14]. Prescribed as a vaginal cream during pregnancy, this treatment can eradicate vaginosis in 76% of cases [14,21-24]. Administered orally for 5 days, the dose of 600 mg used in our trial leads to eradication of bacterial vaginosis in 90% of cases [14,25]. Reports of success using shorter treatment durations [24,26] led us to choose four-day courses of treatment. Our results also confirmed that clindamycin doubles the risk of side effects, especially diarrhea and abdominal pain [14,25]. Nonetheless, the treatment compliance in our study, estimated at 78%, is equivalent to that reported in earlier trials [26-28].

In our trial, clindamycin treatment began at a mean gestational age of 12 weeks, and 95% of the women began before 15 weeks. This is a key point because the meta-analysis of five trials by Lamont et al. shows that when clindamycin is prescribed and administered before 22 weeks, it can reduce preterm delivery by 40% and late miscarriages by 80% 24. In the only trial performed with oral clindamycin, Ugwumadu et *al.* showed a reduction of two-thirds in the rate of spontaneous preterm delivery and late miscarriages [25]. Despite oral treatment at an appropriate dosage beginning before 15 weeks and repeated twice in half the cases, we found no reduction in the preterm delivery rate. Our results thus disagree with the favorable conclusions reached by Lamont et *al.*; instead our results provide robust evidence supporting the conclusions of the Cochrane Database meta-analysis [14]. Indeed, this review provided little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent preterm birth and its consequences. It found that antibiotic treatment of bacterial vaginosis did not reduce preterm birth, even when treatment began before 20 weeks. Additionally, our study did not find a trend toward a reduced risk of late miscarriage [14].

The main limitation to our trial is the low prevalence of preterm delivery in our population. The study participants had no history of late miscarriage or of spontaneous preterm delivery and were thus at low risk of preterm birth. Our results are nonetheless essential for discussing the usefulness of screening for and treating bacterial vaginosis during pregnancy. Indeed, as in our cohort, 90% of the women in developed countries have no history of preterm delivery [3,20]. Nonetheless, more than 70% of preterm births occur in in women that had no past history of

preterm birth, despite their low-risk status [3,4]. Accordingly, strategies for preventing preterm delivery cannot ignore this large fraction of pregnant women [29].

Finally, while the infectious origin, ascending from the vagina, of a portion of very preterm deliveries is no longer in doubt 1, our trial shows that antibiotic treatment – even repeated – of anomalies of the vaginal flora in bacterial vaginosis does not reduce the risk of preterm delivery and late miscarriage. In an era increasingly recognizing that indiscriminate antibiotic use increases the risk of resistance and may be associated long-term risks to the child [30], the prospect of screening and simple, safe, inexpensive antibiotic treatment to prevent preterm delivery is growing more distant.

Contributors

DS, GB, FC, CH, EG, KF, BG, EK, RD wrote the first draft. ET, PD prepared the data and performed the statistical analysis. JC, MJ, DD, CD, SD, AP, EJ collected data. AF, MCB, JCD, CN, SG, JLP, PYA, FG contributed to the design and management of the study. All authors contributed to the manuscript revision.

Declaration of interests

None. PFIZER, Inc. (Pfizer France, Paris, France) generously provided the funding to purchase the clindamycin and placebos (packaged for the study by LC2 Pharma©) and had no other involvement in any aspect of the trial.

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	Clindamycin			Placebo
	1 course n=943	**3 courses n=968**	**Total n=1911**	**n=958**
Weeks of gestation at randomization	12·3· ± 2·2	12·4 ± 2·1	12·3 ± 2·2	12·4 ± 2·1
Maternal age – years	27·9 ± 5·4	28·0 ± 5·4	28·0 ± 5·4	27·7 ± 5·5
Educational level				
Primary school	85 (9·0)	82 (8·5)	167 (8·7)	90 (9·4)
High school or technical school	399 (42·4)	459 (47·5)	858 (45·0)	418 (43·8)
Higher education	458 (48·6)	425 (44·0)	883 (46·3)	446 (46·8)
Nulliparous	471 (50·0)	498 (51·8)	969 (50·9)	521 (54·7)
Smoking at the beginning of pregnancy	323 (34·2)	346 (35·7)	669 (35·0)	287 (30·0)
History of miscarriage < 16 weeks	207 (22·1)	195 (20·2)	402 (21·1)	174 (18·3)
History of induced preterm labor (22–36 weeks)	17 (1·8)	16 (1·7)	33 (1·7)	14 (1·5)
History of perinatal death	8 (0·8)	6 (0·6)	14 (0·7)	4 (0·4)
Multiple pregnancy	20 (2·1)	18 (1·9)	38 (2·0)	15 (1·6)
Twins	17	17	34	14
Triplets	3	1	4	1
Nugent score 9 or 10	58 (6·1)	65 (6·7)	123 (6·4)	71 (7·4)

Data are n (%)

Table 1: Baseline Characteristics of Women According to Study Group

	Clindamycin			Placebo	*p*
	1 course n=941	**3 courses n=963**	**Total n=1904**	**n=956**	
Side effects (any)	25 (2·6)	33 (3·4)	58 (3·0)	12 (1·3)	0·003
Diarrhea	14 (1·5)	16 (1·6)	30 (1·6)	4 (0·4)	0·007
Abdominal pain	5 (0·5)	4 (0·4)	9 (0·5)	0 (0·0)	0·03
Other	9 (0·9)	15 (1·5)	24 (1·3)	8 (0·8)	0·31
Incomplete treatment-stopped the protocol	182 (19·3)	192 (19·8)	374 (19·6)	156 (16·3)	0·03
Spontaneous miscarriage < 16 weeks	11 (1·2)	12 (1·2)	23 (1·2)	10 (1·1)	0·70
Elective abortion or termination of pregnancy for medical reasons ≤ 21 weeks*	3 (0·3)	6 (0·6)	9 (0·5)	3 (0·3)	0·53
Termination of pregnancy for medical reasons >= 22 weeks*	3 (0·3)	2 (0·2)	5 (0·3)	5 (0·3)	0·32
Bleeding during second or third trimester	51 (5·5)	52 (5·5)	103 (5·5)	49 (5·2)	0·76
Threatened preterm delivery (hospitalization)	71 (7·7)	93 (9·8)	164 (8·8)	80 (8·5)	0·85
Abruptio placentae	5 (0·5)	8 (0·8)	13 (0·7)	11 (1·2)	0·20
Prenatal signs of chorioamnionitis **	14 (1·5)	10 (1·1)	24 (1·3)	8 (0·9)	0·31
Premature rupture of the membranes ≥ 12 h	147 (16·0)	128 (13·5)	275 (14·7)	141 (15·0)	0·82
< 37 weeks	21 (2·3)	21 (2·2)	42 (2·2)	18 (1·9)	0·57
≥ 37 weeks	126 (13·5)	107 (11·2)	233 (12·3)	123 (13·0)	0·63

Data are n (%)

* In the case of multiple pregnancies, selective termination of one fetus is not considered

** At least two signs among the following: maternal fever > 38°C, vaginal bleeding before labor, purulent foul-smelling vaginal discharge, maternal tachycardia > 100 BPM, fetal tachycardia > 160 BPM, maternal CRP= 15 mg/L, maternal leukocytes =15 × 10 9/L

Table 2: Events during pregnancy

	Clindamycin			Placebo	*p*	Relative risk (95% CI)
	1 course n=941	3 courses n=963	Total n=1904	n=956		
Primary outcome						
Late miscarriage or spontaneous very preterm delivery 16-32^{+6} *	8 (0·8)	14 (1·4)	22 (1·2)	10 (1·0)	0·82	1·10 (0·53-2·32)
16-21^{+6}	4 (0·4)	10 (1·0)	14 (0·7)	2 (0·2)	†	
22-32^{+6}	4 (0·4)	4 (0·4)	8 (0·4)	8 (0·8)	‡	
Preterm delivery 22-36^{+6}	62 (6·6)	66 (6·8)	128 (6·7)	56 (5·8)	0·37	1·15 (0·85-1·56)
Spontaneous	43 (4·6)	48 (5·0)	91 (4·8)	39 (4·1)	0·40	1·17 (0·81-1·69)
Induced	19 (2·0)	18 (1·9)	37 (1·9)	17 (1·8)	0·76	1·09 (0·62-1·93)
Miscarriage < 15^{+6}	11	12	10	23		
Termination or preg· or legal abortion ≤ 21^{+6}*	3	6	3	9		
Termination or preg· ≥22*	3	2	5	5		
Fetal death ≥22 wks of one or both fetuses *	3	4	7	4		
Delivery of liveborn child ≥ 22 weeks **	917 (97·4)	929 (96·5)	1846 (97·0)	932 (97·5)	0·42	0·82 (0·51-1·33)
Gestational age at delivery **	38·8 ± 4·1	38·6 ± 4·5	38·7 ± 4·3	38·9 ± 3·9	0·92	
Cesarean	89 (9·6)	109 (11·5)	198 (10·6)	96 (10·2)	0·93	1·05 (0·81-1·36)
Cesarean before labor	78 (8·4)	76 (8·1)	154 (8·3)	89 (9·5)	0·27	0·86 (0·65-1·13)
Fever during labor	22 (2·4)	37 (3·9)	59 (3·2)	31 (3·3)	0·83	0·95 (0·61-1·48)
Postpartum fever	26 (2·8)	31 (3·3)	57 (3·1)	24 (2·6)	0·46	1·20 (0·74-1·94)
Post-partum wound infection	3 (0·3)	4 (0·4)	7 (0·4)	3 (0·3)	> 0·99	1·17 (0·30-4·52)

Data are n (%)

* In the case of multiple pregnancies, selective termination of one fetus is not considered

** At least one liveborn child, fetal death and TOP excluded

† Not significant (p=0·07), ‡ Not significant (p=0·16)

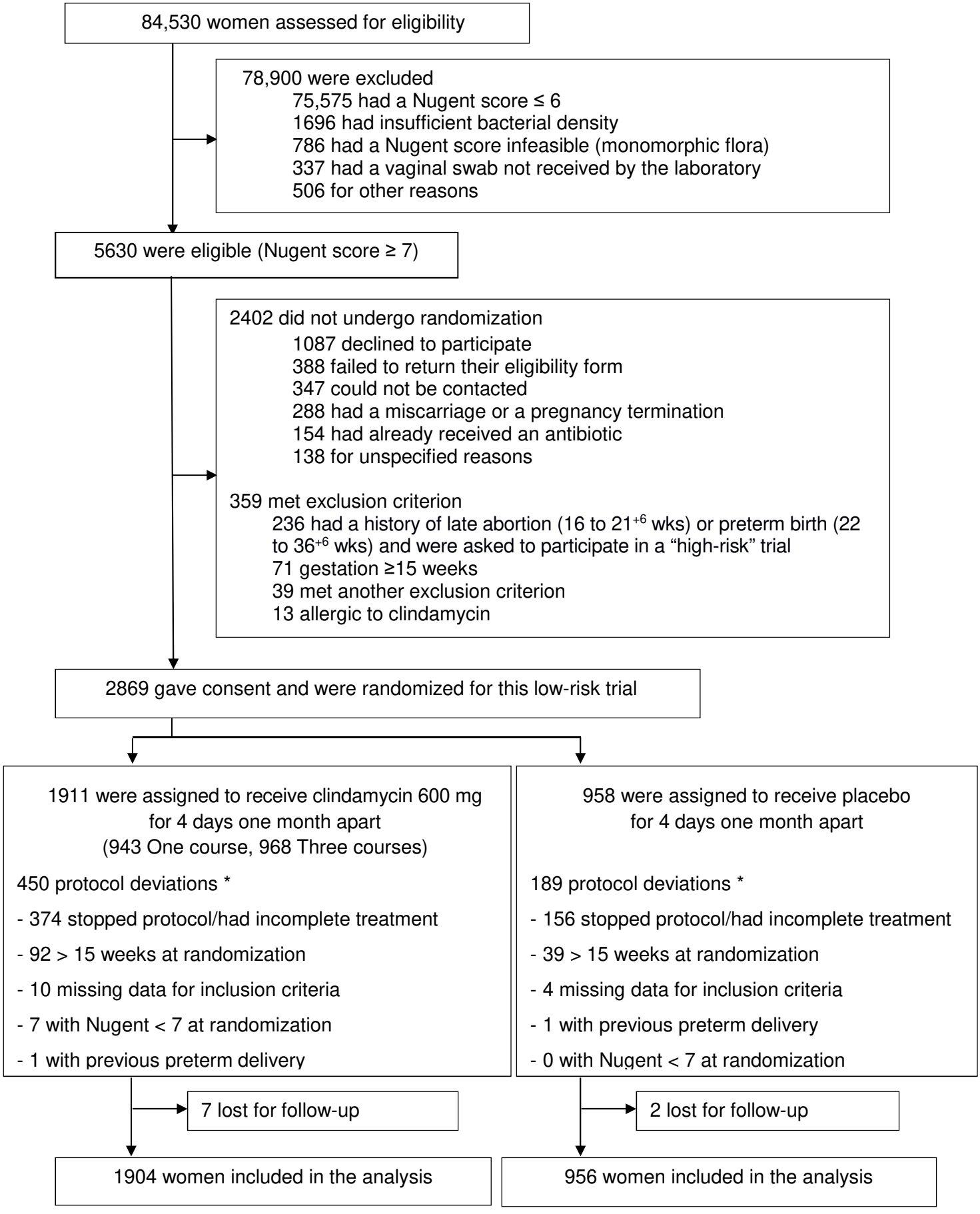
Table 3: Pregnancy outcomes (mothers)

	Clindamycin			Placebo	*p*	Relative risk (95% CI)
	1 course n=945	**3 courses n=953**	**Total n=1898**	**n=955**		
Termination of pregnancy for medical reasons ≥ 22 weeks*	3 (0·3)	2 (0·2)	5 (0·3)	6 (0·6)	0·20	0·42 (0·13- 1·37)
Fetal death ≥ 22 weeks**, [a]	4 (0·4)	5 (0·5)	9 (0·5)	6 (0·6)	0·59	0·75 (0·27-2·11)
Live born ≥ 22 weeks	938 (99·3)	946 (99·3)	1884 (99·3)	943 (98·7)	0·17	1·01 (1·0 -1·01)
Gestational age***	39·3 ± 2·1	39·3 ± 2·0	39·3 ± 2·0	39·4 ± 1·9	0·95	
Less than 32^{+6} weeks	18 (1·9)	9 (1·0)	27 (1·4)	12 (1·3)	0·73	1·13 (0·57-2·21)
Less than 36^{+6} weeks	78 (8·3)	76 (8·0)	154 (8·2)	71 (7·5)	0·55	1·09 (0·83-1·42
Birth weight***	3260 ± 600	3250 ± 560	3250 ± 580	3260 ± 550	0·93	
Less than 1500 g	16 (1·7)	9 (1·0)	25 (1·3)	6 (0·6)	0·10	2·09 (0·86-5·07)
Less than 2500 g	80 (8·5)	80 (8·5)	160 (8·5)	75 (8·0)	0·62	1·07 (0·82-1·39)
Neonatal sepsis (suspected or proved)****	21 (2·2)	27 (2·8)	48 (2·5)	31(3·3)	0·27	0·77 (0·49-1·22)
Admission to neonatal intensive care unit	71 (7·6)	70 (7·4)	141 (7·5)	59 (6·3)	0·23	1·20 (0·89 – 1·60)
Perinatal death *****, [a+b]	6 (0·6)	6 (0·6)	12 (0·6)	8 (0·8)	0·53	0·75 (0·31-1·83)
Neonatal death or severe neonatal morbidity [c]	6 (0·6)	6 (0·6)	12 (0·6)	5 (0·5)	0·72	1·20 (0·42 – 3·40)
Neonatal death ≥ 22 weeks [b]	2	1	3	2		
Severe lesions on transfontenellar US	5	1	6	0		
Oxygen therapy ≥ 36 weeks	1	4	5	4		
Poor perinatal outcome [a+c]	10 (1·1)	11 (1·1)	21 (1·1)	11 (1·2)	0·91	0·96 (0·46-1·97)

Data are n (%)
* In the case of multiple pregnancies, selective termination of one fetus is not considered
** In the case of multiple pregnancies, in utero death of one fetus is not considered
*** In utero death and termination of pregnancy for medical reasons ≥ 22 weeks* excluded
**** Suspected: C reactive protein > 15 mg/L with positive peripheral samples· Proved: positive blood culture or CSF or trachea samples
***** Fetal death ≥ 22 weeks of gestation or neonatal death in the first month of life, termination excluded

Table 4: Fetal and Neonatal outcomes according to maternal treatment assignment (birth ≥ 22 weeks)

Figure 1. Flow Chart



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