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

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Summary

Background **Preterm delivery during pregnancy (<37 weeks' gestation) is a leading cause of perinatal mortality and morbidity. Treating bacterial vaginosis during pregnancy can reduce poor outcomes, such as preterm birth. We aimed to investigate whether treatment of bacterial vaginosis decreases late miscarriages or spontaneous very preterm birth.**

Methods **PREMEVA was a double-blind randomised controlled trial done in 40 French centres. Women aged 18 years or older with bacterial vaginosis and low-risk pregnancy were eligible for inclusion and were randomly assigned (2:1) to three parallel groups: single-course or triple-course 300 mg clindamycin twice-daily for 4 days, or placebo. Women with high-risk pregnancy outcomes were eligible for inclusion in a high-risk subtrial and were randomly assigned (1:1) to either single-course or triple-course clindamycin. The primary outcome was a composite of late miscarriage (16–21 weeks) or spontaneous very preterm birth (22–32 weeks), which we assessed in all patients with delivery data (modified intention to treat). Adverse events were systematically reported. This study is registered with ClinicalTrials.gov, number NCT00642980.**

Findings **Between April 1, 2006, and June 30, 2011, we screened 84 530 pregnant women before 14 weeks' gestation. 5630 had bacterial vaginosis, of whom 3105 were randomly assigned to groups in the low-risk trial (n=943 to receive single-course clindamycin, n=968 to receive triple-course clindamycin, and n=958 to receive placebo) or high-risk subtrial (n=122 to receive single-course clindamycin and n=114 to receive triple-course clindamycin). In 2869 low-risk pregnancies, the primary outcome occurred in 22 (1·2%) of 1904 participants receiving clindamycin and 10 (1·0%) of 956 participants receiving placebo (relative risk [RR] 1·10, 95% CI 0·53–2·32; p=0·82). In 236 high-risk pregnancies, the primary outcome occurred in 5 (4·4%) participants in the triple-course clindamycin group and 8 (6·0%) participants in the single-course clindamycin group (RR 0·67, 95% CI 0·23–2·00; p=0·47). In the low-risk trial, adverse events were more common in the clindamycin groups than in the placebo group (58 [3·0%] of 1904 *vs* 12 [1·3%] of 956; p=0·0035). The most commonly reported adverse event was diarrhoea (30 [1·6%] in the clindamycin groups *vs* 4 [0·4%] in the placebo group; p=0·0071); abdominal pain was also observed in the clindamycin groups (9 [0·6%] participants) versus none in the placebo group (p=0·034). No severe adverse event was reported in any group. Adverse fetal and neonatal outcomes did not differ significantly between groups in the high-risk subtrial.**

Interpretation **Systematic screening and subsequent treatment for bacterial vaginosis in women with low-risk pregnancies shows no evidence of risk reduction of late miscarriage or spontaneous very preterm birth. Use of antibiotics to prevent preterm delivery in this patient population should be reconsidered.**

Funding **French Ministry of Health.**

Introduction

Preterm delivery (ie, livebirth before 37 weeks of pregnancy are completed), is the leading cause of perinatal mortality and morbidity worldwide.[1,2] 70% of preterm deliveries occur in women with no history of preterm delivery.[3,4]

Preterm delivery can be individualised into subgroups on the basis of 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 delivery lead to a high rate of neurological and respiratory complications in newborn babies.[2]

Although preterm deliveries are multifactorial, including major risk factors such as smoking or ethnicity, several clinical studies have found an association between preterm delivery and bacterial vaginosis.[5–7] Bacterial vaginosis is an excessive growth of certain vaginal bacteria leading to a major imbalance of the vaginal microbiota, characterised by a decreased abundance of *Lactobacillus* species and an increased abundance of anaerobes and

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Research in context

Evidence before this study

When we planned our study in 2005, the meta-analysis of Leitich and colleagues (2003) had shown a strong association between bacterial vaginosis and preterm birth before 37 weeks (odds ratio 2·19, 95% CI 1·54–3·12).

The same year, Ugwumadu and colleagues published the results of a large randomised controlled trial, in which participants received either clindamycin 300 mg or placebo orally, twice-daily for 5 days. The authors showed a significant reduction in miscarriages or spontaneous preterm birth in the clindamycin group. These results were taken into account in a 2005 Cochrane meta-analysis, which showed the need to focus on early detection and treatment of bacterial vaginosis in large trials. We searched PubMed using the terms "bacterial vaginosis" and "preterm birth", for articles published before 2006.

While enrolment in this study was ongoing, two meta-analyses reported conflicting results for use of clindamycin in this patient population. Lamont and colleagues showed a significantly reduced risk of preterm birth before 37 weeks and late miscarriage when clindamycin was given before 22 weeks' gestation to women with bacterial vaginosis; Brocklehurst and colleagues showed no difference for any preterm birth.

Added value of this study

To our knowledge, PREMEVA is the only large trial in this field. We screened 84 530 pregnant women before 14 weeks' gestation and randomly allocated 2869 women with bacterial vaginosis to receive clindamycin or placebo. This strategy also does not reduce late miscarriage or preterm birth before 33 weeks or 37 weeks.

Implications of all the available evidence

Future guidelines should take these results into account. The findings from PREMEVA provide support for the national recommendations that asymptomatic women without a history of previous early delivery should not be screened or treated for bacterial vaginosis.

genital mycoplasmas. Bacterial vaginosis can be diagnosed either clinically, with the Amsel criteria [8] (ie, presence of clue cells, a vaginal pH greater than 4·5, profuse white discharge, and a fishy odour when the vaginal discharge is exposed to potassium hydroxide), or microbiologically, with the Nugent score.[9] The Nugent score establishes the decrease in *Lactobacillus* species and the increase in anaerobes on a Gram-stained vaginal smear. The Nugent score can be more reproducible than the Amsel criteria in a clinical study.[10] The prevalence of bacterial vaginosis varies worldwide, and was estimated to be 7·1% (95% CI 6·6–7·5%) in a cohort of 14193 pregnant women in the Nord-Pas de Calais region of France, with the Nugent score.[9]

During pregnancy, bacterial vaginosis increases the risk of preterm delivery by more than two times (odds ratio [OR] 2·19, 95% CI 1·54–3·12).[11] Results from a meta-analysis[11] show that this risk can increase more than four times when bacterial vaginosis is identified before 20 weeks of gestation (4·20, 2·11–8·39) and seven times when bacterial vaginosis is identified before 16 weeks of gestation (7·55, 1·80–31·65). Additionally, bacterial vaginosis can increase the risk of spontaneous abortion more than nine times (9·91, 1·99–49·34) and the risk of maternal infection more than two times (2·53, 1·26–5·08).[11] However, the pathophysiological mechanisms through which bacterial vaginosis affects ongoing pregnancy remain unclear. The imbalance of vaginal microbiota occurring during bacterial vaginosis might lead to vaginal infection that could ascend into the uterus early during pregnancy.[12] Therefore, it has been hypothesised that early antibiotic treatment of bacterial vaginosis during pregnancy might prevent some preterm deliveries.

Since the 1990s, several antibiotic regimens have been studied in pregnant women with bacterial vaginosis in randomised controlled trials. Two recent meta-analyses have contradictory findings.[13,14] One concluded that clindamycin prescribed before 22 weeks of gestation might reduce the risk of preterm delivery by 40%,[13] whereas the other found no reduction at all, even when antibiotics were initiated before 20 weeks' gestation.[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 randomised controlled trial designed to test the effectiveness of early clindamycin in reducing the rate of late miscarriages or births before 32 weeks in women with low-risk pregnancies with bacterial vaginosis during the first trimester, and to test the effectiveness of single-course versus triple-course clindamycin in high-risk patients.

Methods

Study design and participants

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, with self-collected vaginal samples.[15] Bacterial vaginosis was defined by a Nugent score of 7 or higher with these samples. Women with bacterial vaginosis and at low risk of preterm delivery (with no history of either late miscarriage from 16 to 21 weeks and 6 days or preterm delivery from 22 to 36 weeks and 6 days) were asked to participate in a randomised, multicentre, placebo-controlled double-blind trial at 40 participating centres.

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Participants were eligible if they were aged 18 years or older, had a gestational age less than 15 weeks, and were able to speak French and provide written informed consent. Participants were excluded if they had a known allergy to clindamycin, vaginal bleeding within the week before proposed screening of bacterial vaginosis, or planned to give birth in a different region.

Women at high risk of preterm delivery (with a history of late miscarriage from 16 to 21 weeks and 6 days, or preterm delivery from 22 to 36 weeks and 6 days) were offered the choice of participating in a subtrial.

Informed consent of eligible participants was obtained at two steps: first, for the screening of bacterial vaginosis with self-collected vaginal samples and second, after obtaining screening results before random allocation into study groups. This approach was also used in the high-risk subtrial.

The regional institutional review board approved the study (Comité de Protection des Personnes participant à la Recherche Biomédicale—PHRC2004/1918 PROM04-06-859).

Randomisation and masking

Women with low-risk pregnancies were randomly assigned (2:1) with a computer-generated random allocation sequence with a block size of six (T4trials/T4fields, Paris, France) to three parallel groups (single-course clindamycin, triple-course clindamycin, and placebo). Participants received a numbered box corresponding to their randomisation sequence. Each box contained three blister packs numbered from 1 to 3, each containing eight capsules of study drug (clindamycin) or placebo. Study participants and all health-care professionals were masked to the composition of the boxes: a third contained exclusively 300 mg clindamycin capsules (triple-course), a third contained 300 mg clindamycin capsules in blister pack number one and placebo in the other two blister packs (single-course), 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). Randomisation was stratified by centre. The randomisation list was kept by the study kit manufacturer. Participants were instructed to begin treatment the day after randomisation and use the blister packs in their numbered order. Use of other treatments, including antibiotics, was permitted during the study period. The Nugent score was not reassessed during pregnancy.

Women with high-risk pregnancy outcomes were randomly assigned (1:1) to either single-course or triple-course clindamycin without any placebo group because of ethical considerations, according to French ethics guidelines.[16] These subtrial participants were recruited and consented using the same screening method, during the same period as the other participants.

Procedures

Each woman took a vaginal self-sample with one swab in a screening centre. Nugent scoring by Gram-staining was done in the laboratory within 4 h of sample self-collection. Nugent scores were determined as described elsewhere.[9] Scores of 0–3 were considered normal (*Lactobacillus*-dominant), 4–6 were labelled as intermediate (mixed morphotypes), and 7–10 were indicative of bacterial vaginosis (absence of *Lactobacilli* and predominance of the other two morphotypes).

In the low-risk trial, the regimen was one capsule to be taken orally morning and evening for 4 days, once a month for 3 months. Participants received one 4-day course of 300 mg oral clindamycin twice-daily, followed by two 4-day courses of placebo twice-daily, spaced 1 month apart (single-course clindamycin); three 4-day courses of 300 mg clindamycin twice-daily, spaced 1 month apart (triple-course clindamycin); or placebo. Patients with high-risk pregnancies enrolled in the subtrial were given one course of clindamycin versus three courses of clindamycin (as defined previously).

Outcomes

The primary outcome was a composite of the onset of spontaneous late miscarriage (between 16 and 21 weeks) or spontaneous very preterm delivery (between 22 and 32 weeks), regardless of whether the newborn baby was alive. Late miscarriage and very preterm deliveries were considered spontaneous if they followed the spontaneous onset of labour or premature rupture of the membranes (PROM), regardless of final method of delivery.

The secondary outcomes were hospitalisation for threatened preterm delivery, hospitalisation for PROM, number of days of hospitalisation for preterm PROM (PPROM) or PROM, prenatal signs of chorioamnionitis (at least two signs from: maternal fever >38°C, vaginal bleeding before labour, purulent foul-smelling vaginal discharge, maternal tachycardia >100 beats per min, fetal tachycardia >160 beats per min, maternal C-reactive protein of 15 mg/L, maternal leucocytes of 15×10^9/L), abruptio placentae, PROM (<37 weeks and ≥37weeks), preterm delivery at 22–36, plus 6 days (spontaneous or induced), hyperthermia during labour (≥38°C), maternal post-partum fever (≥38°C), abscess of abdominal wall or episiotomy (post-partum), and need for antibiotic treatment more than 24 h after delivery.

Fetal and neonatal outcomes (≥22 weeks) were: fetal death at 22 weeks or later (termination of pregnancy for medical reasons ≥22 weeks was excluded), admission to the neonatal intensive care unit, neonatal pulmonary disease (need for ventilation ≥24 h, duration of ventilation in days, oxygen therapy ≥36 weeks), suspected neonatal sepsis (C-reactive protein >15 mg/L with positive peripheral samples) or proved neonatal sepsis (positive blood culture, CSF, or trachea samples), severe lesions on transfontanellar ultrasonography, and neonatal death at 22 weeks or later, defined as early

(0–6 days), late (7–28 days), and more than 28 days before discharge.

Statistical analysis

In both the low-risk and high-risk studies, we compared all outcomes between the placebo group and both (single-course or triple-course) clindamycin groups combined. In case of a significant difference between both clindamycin groups and the placebo group, each clindamycin group was compared with the other in a planned supplemental analysis to determine the efficacy of repeated versus single courses of clindamycin. In the high-risk subtrial, all outcomes were compared between single-course and triple-course clindamycin groups given the absence of placebo. No interim analyses were planned. In France, the proportion of preterm deliveries before 32 weeks and late miscarriages from 16 to 21 weeks is estimated at approximately 2%,[17] 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. Because we expected a reduction of 50% with antibiotic treatment,[13,18] we calculated that the sample size should identify a reduction in the incidence of late miscarriage or spontaneous preterm delivery of 2% in the combined clindamycin groups. 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 combined clindamycin groups. With a prevalence of bacterial vaginosis estimated at 5–10%, we needed to screen at least 80 000 women. The trial took place in a region of more than 4 million inhabitants, where approximately 58 000 children are born each year, 6·9% of them preterm.[17] In the high-risk sub-population, given the lack of published data, calculation of a number needed to treat was not possible, and the single-course versus triple-course comparison was considered to be an observational pilot sub-study.

Participant data were collected at inclusion and after delivery. In addition to outcomes, planned data collection included adverse effects of clindamycin (such as diarrhoea, defined as having at least three daily episodes of liquid stool, abdominal pain, or any other complaint), incomplete treatment (stopped the protocol), liveborn at 22 weeks or later, gestational age and birthweight (excluding in-utero death and termination of pregnancy for medical reasons ≥22 weeks), number of perinatal deaths (fetal death ≥22 weeks of gestation or neonatal death in the first week of life), and antibiotic treatment(s) received during the pregnancy.

To verify the spontaneous or induced nature of deliveries, each pregnancy outcome before 37 weeks was systematically reviewed by four study investigators (two obstetricians [GB, DS] and two midwives [SD, AP], all masked to treatment allocation). An independent data safety committee monitored the trial.

To estimate compliance, we planned to contact by phone at least 5% of consecutive women included in the study at the beginning of their third trimester. We also collected oral statements at each visit. We did a per-protocol analysis of patients who gave back their treatment box at the end of the study with at least the first blister pack empty, to assess whether compliance with study treatments modified the results.

The database was frozen in April, 2013, before unmasking of investigators. Data from all participants were independently analysed according to the group to which they were randomly assigned. The analysis was modified intention to treat, excluding women lost to follow-up. In the high-risk subtrial, the analysis was modified intention to treat, excluding women without delivery data.

We compared categorical variables using the χ^2 test, and continuous variables using Student's *t* test, Fisher's exact test, and Kruskal-Wallis test

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 the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 1, 2006, and June 30, 2011, we screened 84 530 pregnant women from whom vaginal sample smears were obtained and Nugent scores determined. Of 5630 women eligible for the study (Nugent score ≥7), 2402 were not randomly assigned and 123 met exclusion criteria (figure). Thus, 2869 were included in the low-risk trial and randomly assigned to receive clindamycin (n=943 received one course and n=968 received three courses) or placebo (n=958). 236 women were included in the high-risk subtrial and were randomly assigned to receive clindamycin (n=122 to one course and n=114 to three courses). The last woman included in the trial gave birth on Feb 1, 2012.

Median gestational age at randomisation was 12·4 weeks (SD 2·1) and half of the participants were nulliparous (table 1). There were 53 multiple pregnancies, including five sets of triplets (table 1). The incidence of Nugent scores of 9 or 10 was 6·4% in the clindamycin groups and 7·4% in the placebo group (table 1).

The incidence of the primary outcome in the modified intention-to-treat population was 1·2% in the clindamycin groups and 1·0% in the placebo group (p=0·82; table 2). Preplanned analyses showed that none of the secondary outcomes among mothers and among newborn babies differed significantly between the two groups (tables 2, 3). The groups had similar rates of spontaneous preterm delivery between 22 and 36 weeks' gestation (4·8% in the clindamycin group and 4·1% in

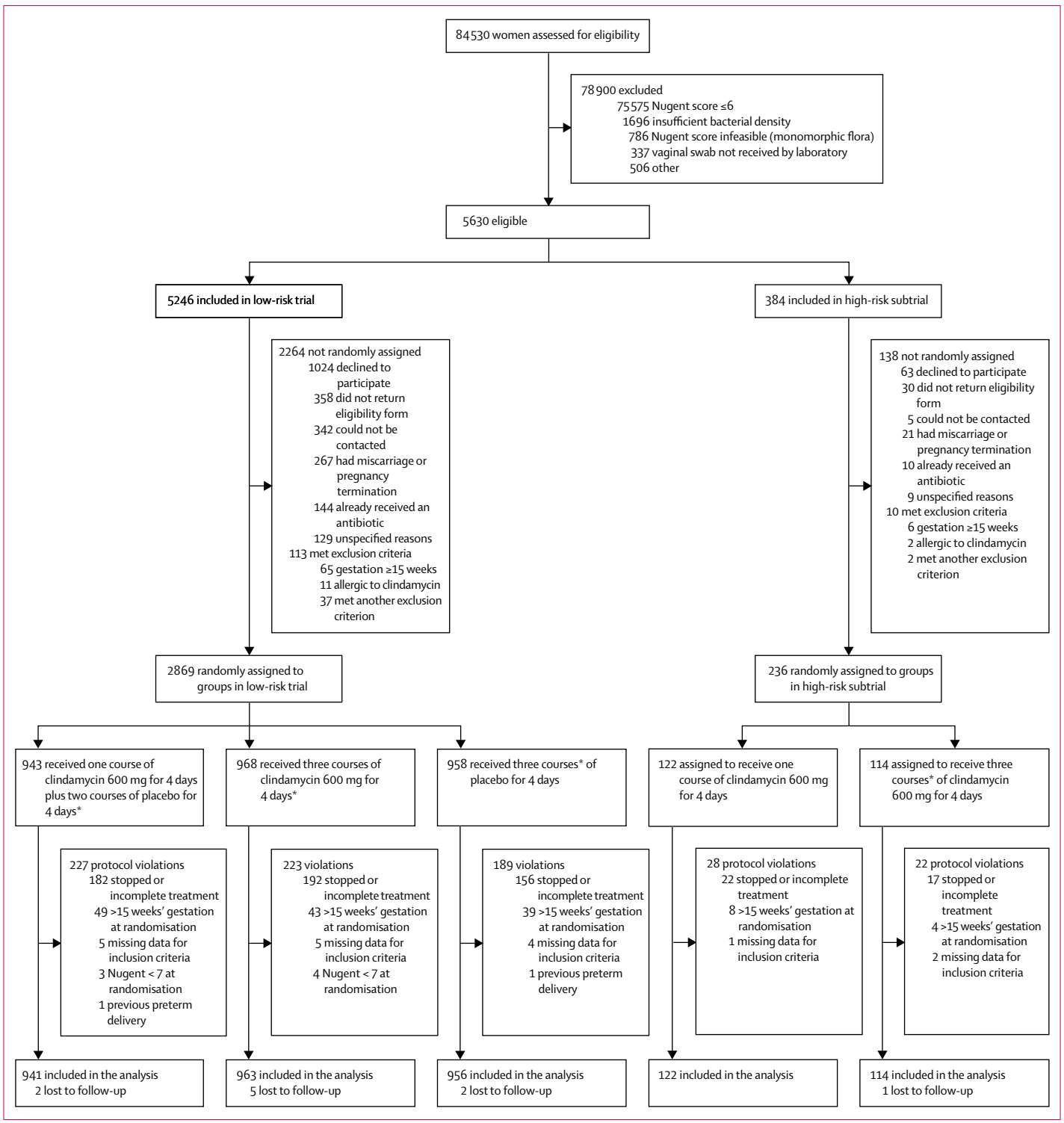

Figure: **Trial profile**
*Each course in the low-risk and high-risk trial was 1 month apart.

the placebo group) and total preterm delivery (6·7% in the clindamycin group and 5·9% in the placebo group, respectively; table 2).

We did a per-protocol analysis of the 1409 (49·1%) of the study participants for whom compliance of treatment was verifiable by pill-counting at the end of pregnancy. This

	Clindamycin			Placebo (n=958)
	One course (n=943)	Three courses (n=968)	Total (n=1911)	
Mean gestational age at randomisation, weeks	12·3 (2·2)	12·4 (2·1)	12·3 (2·2)	12·4 (2·1)
Mean 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 (42·3%)	459 (47·4%)	858 (44·9%)	418 (43·6%)
Higher education	458 (48·6%)	425 (43·9%)	883 (46·2%)	446 (46·6%)
Nulliparous	471 (49·9%)	498 (51·4%)	969 (50·7%)	521 (54·3%)
Smoking at the beginning of pregnancy	323 (34·2%)	346 (35·7%)	669 (35·0%)	287 (30·0%)
History of miscarriage <16 weeks	207 (22·0%)	195 (20·1%)	402 (21·0%)	174 (18·2%)
History of induced preterm labour (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	17/20 (85·0%)	17/18 (94·4%)	34/38 (89·5%)	14/15 (93·3%)
Triplets	3/20 (15·0%)	1/18 (5·6%)	4/38 (10·5%)	1/15 (6·7%)
Nugent score 9 or 10	58 (6·2%)	65 (6·7%)	123 (6·4%)	71 (7·4%)

Data are n (%), n/N (%), or mean (SD).

Table 1: **Baseline characteristics of the intention-to-treat population**

per-protocol analysis did not differ from the study findings regarding primary and secondary outcomes (appendix).

Adverse events were reported by 58 (3·0%) of participants in the clindamycin groups and 12 (1·3%) of 956 participants in the placebo group (p=0·0035; table 4). The most commonly reported adverse event was diarrhoea (30 [1·6%] in the clindamycin groups *vs* 4 [0·4%] in the placebo group; p=0·0071); abdominal pain was also observed in the clindamycin groups (9 [0·6%] participants) versus none in the placebo group (p=0·034). No severe adverse event was reported in any group. The percentage of women who stopped taking the study treatment was higher in the clindamycin than the placebo group (374 [19·6%] *vs* 156 [16·3%]; p=0·031). Adverse fetal and neonatal outcomes did not differ significantly between the clindamycin and placebo groups, nor did they differ for neonatal weight less than 1500 g (25 [1·3%] of 1898 *vs* 6 [0·6%] of 955; p=0·10), neonatal weight less than 2500 g (160 [8·4%] *vs* 75 [7·9%]; p=0·62), and perinatal death (11 [0·6%] *vs* 7 [0·7%]; p=0·63; table 4).

Over a 38-day period, 247 consecutive women were contacted by phone to estimate compliance, accounting for 8·6% of the 2869 women included in the study. Of these, eight (3·2%) had a spontaneous first trimester miscarriage, and 137 (57·3%) of 239 had taken at least all the pills of the first course, therefore the estimated overall compliance was 78·2% (95% CI 72·5–83·3).

	Clindamycin			Placebo (n=956)	Relative risk (95% CI); p value
	One course (n=941)	Three courses (n=963)	Total (n=1904)		
Primary outcome					
Late miscarriage or spontaneous very preterm delivery 16–32 weeks (plus 6 days)*	8 (0·8%)	14 (1·5%)	22 (1·2%)	10 (1·0%)	1·10 (0·53–2·32); p=0·82
Secondary outcomes					
Hospitalisation for threatened preterm delivery	71 (7·4%)	93 (9·7%)	164 (8·6%)	80 (8·4%)	1·03 (0·77–1·38); p=0·83
Hospitalisation for premature rupture of membranes ≥24 h	25 (2·7%)	28 (2·9%)	53 (2·8%)	30 (3·1%)	0·88 (0·55–1·44); p=0·29
Mean number of days of hospitalisation for premature PROM or PROM	3·6 (3·6)	4·2 (4·5)	3·9 (4·1)	5·6 (12·7)	NA; p=0·17
Prenatal signs of chorioamnionitis†	14 (1·5%)	10 (1·0%)	24 (1·3%)	8 (0·8%)	1·51 (0·65–3·67); p=0·31
Abruptio placentae	5 (0·5%)	8 (0·8%)	13 (0·7%)	11 (1·2%)	0·59 (0·25–1·42); p=0·20
Premature rupture of the membranes	147 (15·6%)	128 (13·3%)	275 (14·4%)	141 (14·7%)	0·98 (0·78–1·22); p=0·82
<37 weeks	21 (2·3%)	21 (2·2%)	42 (2·2%)	18 (1·9%)	1·18 (0·65–2·13); p=0·57
≥37 weeks	126 (13·4%)	107 (11·1%)	233 (12·2%)	123 (12·9%)	0·94 (0·74–1·20); p=0·63
Preterm delivery 22–36 weeks (plus 6 days)	62 (6·6%)	66 (6·9%)	128 (6·7%)	56 (5·9%)	1·15 (0·85–1·56); p=0·37
Spontaneous	43 (4·6%)	48 (5·0%)	91 (4·8%)	39 (4·1%)	1·17 (0·81–1·69); p=0·40
Induced	19 (2·0%)	18 (1·9%)	37 (1·9%)	17 (1·8%)	1·09 (0·62–1·93); p=0·76
Hyperthermia during labour (≥38°C)	22 (2·3%)	37 (3·8%)	59 (3·1%)	31 (3·2%)	0·95 (0·61–1·48); p=0·83
Maternal postpartum fever (≥38°C)	26 (2·8%)	31 (3·2%)	57 (3·0%)	24 (2·5%)	1·20 (0·74–1·94); p=0·46
Abscess of abdominal wall or episiotomy (post-partum)	3 (0·3%)	4 (0·4%)	7 (0·4%)	3 (0·3%)	1·17 (0·30–4·52); p>0·99
Need for antibiotic treatment >24 h after delivery	112 (11·9%)	108 (11·2%)	220 (11·6%)	113 (11·8%)	0·98 (0·79–1·21); p=0·83

Data are n (%) or mean (SD). PROM=premature rupture of the membranes. NA=not applicable. *For multiple pregnancies, selective termination of one fetus was not considered. †At least two signs among the following: maternal fever greater than 38°C, vaginal bleeding before labour, purulent foul-smelling vaginal discharge, maternal tachycardia greater than 100 beats per min, fetal tachycardia greater than 160 beats per min, maternal C-reactive protein of 15 mg/L, maternal leucocytes of 15×10^9/L.

Table 2: **Pregnancy primary and secondary outcomes in the modified intention-to-treat population**

See Online for appendix

	Clindamycin			Placebo (n=955)	Relative risk (95% CI); p value
	One course (n=945)	Three courses (n=953)	Total (n=1898)		
Fetal death ≥22 weeks	4 (0·4%)	5 (0·5%)	9 (0·5%)	6 (0·6%)	0·75 (0·27–2·11); p=0·59
Admission to neonatal intensive care unit	71 (7·5%)	70 (7·3%)	141 (7·4%)	59 (6·3%)	1·20 (0·89–1·60); p=0·23
Neonatal pulmonary disease					
Need for ventilation (≥24 h)	15 (1·6%)	16 (1·7%)	31 (1·6%)	20 (2·1%)	0·78 (0·43–1·42); p=0·38
Mean duration of ventilation, days	10·7 (17·0)	13·0 (21·6)	11·9 (19·2)	5·2 (9·8)	NA; p=0·10
Oxygen therapy ≥36 weeks	1 (0·1%)	4 (0·4%)	5 (0·3%)	4 (0·4%)	0·60 (0·14–2·64); p=0·48
Neonatal sepsis*	21 (2·2%)	27 (2·8%)	48 (2·5%)	31 (3·3%)	0·77 (0·49–1·22); p=0·27
Suspected	19 (2·0%)	23 (2·4%)	42 (2·2%)	27 (2·9%)	0·78 (0·46–1·31); p=0·31
Proved	2 (0·2%)	4 (0·4%)	6 (0·3%)	4 (0·4%)	0·75 (0·19–3·18); p=0·74
Severe lesions on transfontanellar ultrasonography	5 (0·5%)	1 (0·1%)	6 (0·3%)	0	NA; p=0·19
Neonatal death ≥22 weeks	2 (0·2%)	1 (0·1%)	3 (0·2%)	2 (0·2%)	0·75 (0·10–6·44); p>0·99
Early (0–6 days)	2/2 (100%)	0	2/3 (67%)	1/2 (50%)	..
Late (7–28 days)	0	1/1 (100%)	1/3 (33%)	0	..
>28 days, before discharge	0	0	0	1/2 (50%)	..

Data are n (%), n/N (%), or mean (SD). NA=not applicable. *Suspected sepsis defined as C-reactive protein greater than 15 mg/L with positive peripheral samples; proved defined as positive blood culture, CCSF, or trachea samples.

Table 3: **Fetal and neonatal secondary outcomes according to maternal treatment assignment (≥22 weeks)**

	Clindamycin			Placebo	p value
	One course	Three courses	Total		
Mothers					
Side-effects (any)	25/941 (2·7%)	33/963 (3·4%)	58/1904 (3·0%)	12/956 (1·3%)	0·0035
Diarrhoea	14/941 (1·5%)	16/963 (1·7%)	30/1904 (1·6%)	4/956 (0·4%)	0·0071
Abdominal pain	5/941 (0·5%)	4/963 (0·4%)	9/1904 (0·5%)	0	0·034
Other	9/941 (1·0%)	15/963 (1·6%)	24/1904 (1·3%)	8/956 (0·8%)	0·31
Incomplete treatment	182/941 (19·3%)	192/963 (19·9%)	374/1904 (19·6%)	156/956 (16·3%)	0·031
Newborn babies ≥22 weeks					
Livebirth ≥22 weeks	938/945 (99·3%)	946/953 (99·3%)	1884/1898 (99·3%)	943/955 (98·7%)	0·17
Mean gestational age, weeks*	39·3 (2·1)	39·3 (2·0)	39·3 (2·0)	39·4 (1·9)	0·95
Mean birthweight, g*	3260 (600)	3250 (560)	3250 (580)	3260 (550)	0·93
<1500 g	16/945 (1·7%)	9/953 (0·9%)	25/1898 (1·3%)	6/955 (0·6%)	0·10
<2500 g	80/945 (8·5%)	80/953 (8·4%)	160/1898 (8·4%)	75/955 (7·9%)	0·62
Perinatal death†	6/945 (0·6%)	5/953 (0·5%)	11/1898 (0·6%)	7/955 (0·7%)	0·63

Data are n/N (%) or mean (SD). *In-utero death and termination of pregnancy for medical reasons ≥22 weeks were excluded. †Fetal death ≥22 weeks of gestation or neonatal death in the first week of life.

Table 4: **Other prespecified outcomes during pregnancy, delivery, and the neonatal period**

Using the statements collected at each visit (complete or incomplete treatment), compliance was 80·4% in the clindamycin group versus 83·7% in the placebo group.

Among the 2869 pregnant women randomised, 502 (17·5%) were treated with oral antibiotics during pregnancy. We found no significant difference in antibiotic use between the study groups and results were consistent after we excluded women who had used antibiotics from analyses of the primary or secondary outcomes (appendix). Likewise, the exclusion of multiple pregnancies (n=29) from our analyses had no effect (appendix).

The high-risk subtrial included 236 women with bacterial vaginosis, randomly assigned to receive either single-course (n=122) or triple-course (n=114) clindamycin. These women had much higher rates of preterm delivery (42 [17·9%] of 236) than did women in the placebo group in the low-risk trial (56 [5·9%]; appendix). There were no significant differences in late miscarriage or spontaneous very preterm delivery 16–32 weeks (plus 6 days) between triple-course and single-course clindamycin (5 [4·4%] of 114 *vs* 4 [6·6%] of 122; RR 0·67, 95% CI 0·23–2·00; p=0·47; appendix). Adverse fetal and

neonatal outcomes did not differ significantly between triple-course and single-course clindamycin, nor did they differ for neonatal weight less than 1500 g (6 [5·3%] *vs* 5 [4·2%]; p=0·69), neonatal weight less than 2500 g (29 [25·7%] *vs* 21 [17·6%]; p=0·14), and neonatal death (1 [0·9%] *vs* none; p=0·49; appendix).

Discussion

The PREMEVA trial showed no evidence of a reduction in risk of late miscarriage or spontaneous very preterm delivery after early treatment by oral clindamycin in women at low risk of preterm birth with bacterial vaginosis during the first trimester of pregnancy.

Clindamycin is one of the two most often-used antibiotics to treat bacterial vaginosis during pregnancy.[14] Prescribed as a vaginal cream, this treatment can eradicate vaginosis in 76% of cases.[14,18–21] Administered orally for 5 days, the dose of 600 mg used in our trial normally leads to eradication of bacterial vaginosis in 90% of cases.[14,22,23]

In our trial, clindamycin treatment began at a mean gestational age of 12 weeks, and 95% of the women began before 15 weeks' gestation. This is crucial because the meta-analysis of five trials by Lamont and colleagues[21] showed that when clindamycin is prescribed and administered before 22 weeks, it can reduce preterm delivery by 40% and late miscarriages by 80%. In the only trial done with oral clindamycin, Ugwumadu and colleagues[22] showed a reduction of two-thirds in the rate of spontaneous preterm delivery and late miscarriages. Despite oral treatment at an appropriate dose beginning before 15 weeks and repeated twice in the triple-course group, there was no reduction in the preterm delivery rate. Our results disagree with the favourable conclusions reached by Lamont and colleagues; instead, they provide little evidence that screening and treating all pregnant women with bacterial vaginosis will prevent preterm delivery, and its consequences, when treatment begins before 20 weeks' gestation. Additionally, our findings did not show a reduced risk of late miscarriage.[14]

One limitation of our study might have been compliance. However, compliance was 80·4% in the clindamycin group versus 83·7% in the placebo group. These results are consistent with the 78·2% compliance rate found with phone-call follow-up. Our compliance rates are consistent with those reported in other randomised control trials in the field, ranging from 67·5% in the antibiotic group to 81·3%.[23–25] When taking into account only the most conservative estimation of compliance, in the 49·1% of participants for whom pill-counting was possible, per-protocol analysis was consistent with the study findings regarding primary and secondary outcomes (appendix). Finally, part of the non-compliance was probably due in part to the 3% reported adverse effects. As shown by Ugwumadu and colleagues[22] our results also corroborate that clindamycin doubles the risk of adverse events versus placebo, especially diarrhoea and abdominal pain.[14,22]

Another limitation might be the absence of test-of-cure in the design our study. Indeed, bacterial vaginosis is a relapsing-remitting disease characterised by recurrence, which could decrease the long-term efficiency of antibiotics. Systematic rescreening 1 month after treatment completion, to either ascertain bacterial vaginosis cure or retreat when necessary, has been proposed by several investigators.[18,21,25,26] However, substantial efficacy of clindamycin to treat bacterial vaginosis has been well described and it was more pertinent to design our study with a specific group having three consecutive monthly courses of treatment to ascertain, as much as possible, that at least in this group, treatment of bacterial vaginosis would be optimised, allowing us to dispense with systematic rescreening. There was no difference in study outcomes between groups with single-course or triple-course clindamycin, which is not in favour of mandatory rescreening for bacterial vaginosis treatment failure in preterm birth prevention.

An additional limitation to our trial might also be the low prevalence of very preterm delivery in our population (1·1%), which is inherent to the focus of the study on pregnancies at low risk of preterm delivery. However, this finding was mitigated by results from a large cohort and is essential to discussing the usefulness of screening for and treatment of bacterial vaginosis during pregnancy. Indeed, as in our cohort, 90% of the women in developed countries have no history of preterm delivery.[3,17] Nonetheless, more than 70% of preterm births occur in women who have no history of preterm birth, despite their low-risk status.[3,4] Accordingly, strategies for preventing preterm delivery cannot ignore this large proportion of pregnant women.[27]

Finally, although the infectious origin, ascending from the vagina in most cases of very preterm deliveries, is no longer in doubt,[1] our findings show that antibiotic treatment—even repeated—when bacterial vaginosis is present, shows no evidence in the reduction in risk of preterm delivery and late miscarriage in low-risk pregnancies.

In the context of increasing recognition that indiscriminate antibiotic use increases the risk of resistance and might be associated with long-term risks,[28] antibiotic prevention of preterm delivery in women with low-risk pregnancies who have bacterial vaginosis should be reconsidered. In high-risk pregnancies, there was no benefit of triple-course compared with single-course clindamycin. One option could be to study antibiotic prevention in high-risk pregnancies through a dose-escalation study.

Contributors

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

Declaration of interests

We declare no competing interests. Pfizer Inc (Pfizer France, Paris, France) provided the funding to purchase the clindamycin and placebos

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