Antibiotic therapy in patients with preterm premature rupture of membranes: a prospective, randomized, placebo-controlled study with microbiological assessment of the amniotic cavity and lower genital tract

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ABSTRACT

Objective Preterm premature rupture of membranes (PROM) is responsible for one-third of premature deliveries and is associated with maternal and neonatal morbidity and mortality. Several studies have investigated the role of antibiotic therapy in this group of patients with conflicting results. However, routine microbiological assessment of the lower genital tract and amniotic cavity was not performed in those studies. Our purpose was to test the effect of antibiotics in patients with preterm PROM, according to the presence of microbial invasion of the amniotic cavity (MIAC) and cervicovaginal infection.

Study design Between November 1990 and September 1994, patients with preterm PROM between 24 and 34 weeks, without clinical chorioamnionitis and without labor, were enrolled. Amniocentesis was offered to all patients and the cervix and vagina were sampled for microbiological and cytological studies. Patients were then allocated to receive either clindamycin and gentamicin or placebo for 7 days, and managed expectantly until 35 weeks unless maternal or fetal indications for delivery developed. Contingency tables, *t*-test and non-parametric statistics were used for analysis.

Results Eighty-eight women with preterm PROM were randomly allocated to either antibiotic administration (clindamycin + gentamicin) ($n = 42$) or placebo ($n = 46$). Patients receiving antibiotics had a longer randomization-to-delivery interval than the placebo group (median 10.5 days, range 0–41 vs. median 4 days, range 0–32, respectively; $p < 0.05$). This effect was stronger in patients with cervicovaginal infection only than in patients with cervicovaginal infection and MIAC. No differences were observed when cervicovaginal infection and MIAC were absent. Maternal infectious morbidity was lower in patients who received antibiotics than in patients receiving placebo (4.8% (2/42) vs. 28.9% (13/45), respectively, $p < 0.01$). This effect occurred particularly markedly in the group with MIAC (antibiotic group: 9.1% (2/22) vs. placebo group: 45.5% (10/22), $p < 0.01$). Neonates born to mothers who received antibiotics had a lower rate of respiratory distress syndrome than the placebo group (9.5% (4/42) vs.

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30.2% (13/43), respectively, $p < 0.05$) and admission to the intensive care unit was less frequent (54.8% (23/42) vs. 86.0% (37/43), respectively, $p < 0.01$). Antibiotic therapy did not modify the rate of neonatal infection or mortality.

Conclusions Antibiotic administration to patients with preterm PROM prolongs the duration of pregnancy, and reduces the rate of maternal infection-related morbidity, the neonatal intensive care unit admission rate and the frequency of respiratory distress syndrome.

INTRODUCTION

Preterm premature rupture of membranes (PROM) is the leading identifiable cause of preterm delivery and is associated with increased maternal and neonatal morbidity and mortality[1,2]. There is a growing body of evidence supporting a role for intra-amniotic infection in the pathogenesis of preterm PROM[3]. Micro-organisms are a source of proteases which may contribute to membrane rupture. Moreover, the host response, involving activation of decidual macrophages and neutrophils, can produce proteases and cytokines as well as prostaglandins[4–7]. While expression of degrading proteases is capable of compromising membrane integrity and causing cervical changes, prostaglandins stimulate myometrial contractility.

Previous reports have found that microbial invasion of the amniotic cavity (MIAC) is present in one-third of cases of preterm PROM[7]. Micro-organisms isolated from the amniotic fluid in cases of PROM are similar to those normally found in the lower genital tract (vagina and cervix). This supports the view that microbial invasion of the amniotic cavity follows an ascending pathway.

Several clinical trials have demonstrated that administration of antibiotics to patients with preterm PROM prolongs the duration of pregnancy, but findings regarding the reduction in maternal and neonatal morbidity have been inconsistent[8–16]. The purpose of this study was to investigate (1) the overall efficacy of antibiotic administration in patients with preterm PROM; and (2) the specific effect of this therapy in patients with demonstrated microbial invasion of the amniotic cavity or cervicovaginal infection.

PATIENTS AND METHODS

Patient population

Between November 1991 and September 1994, patients identified as having preterm PROM and a gestational age ranging between 24 and 34 weeks were asked to participate in this study. Figure 1 shows a flow diagram describing the trial profile in accordance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement[17]. Preterm PROM was diagnosed with sterile speculum examination and a combination of pooling, ferning, and nitrazine tests. Amniocentesis was offered to all patients. Since microbiological studies of amniotic fluid were performed immediately after the procedure, only patients admitted during normal working hours were invited to participate in the study. The protocol was approved by the Human Investigation Committee of Hospital San Borja Arriarán. Informed consent was obtained from each participating patient.

Gestational age assessment was based on menstrual history when reliable, pelvic examination in the first trimester consistent with the stated length of amenorrhea, or ultrasonographic fetal biometry before 24 weeks. Assessment of cervical dilatation was made and samples of cervical and vaginal secretions were taken during speculum examination. Digital vaginal examinations were not performed on admission. All patients underwent obstetric

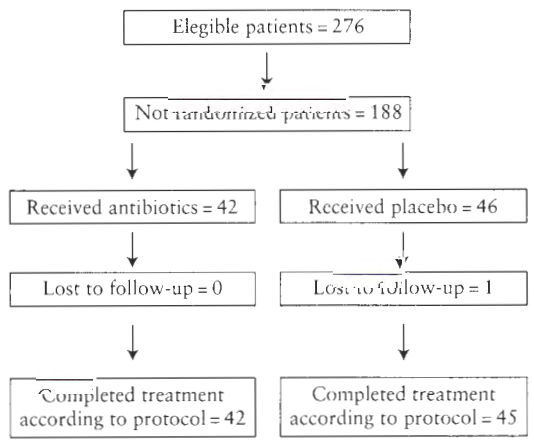

Figure 1 Trial profile and patient compliance with treatment protocol

ultrasound for fetal biometry and amniotic fluid assessment.

Exclusion criteria were as follows: labor, significant hemorrhage, abruptio placentae, use of antibiotics within 30 days before screening for this study, fetal anomaly or death, multiple gestation, documented allergy to clindamycin or gentamicin, uterine anomalies, presence of an intrauterine device, fetal distress, clinical chorioamnionitis, maternal medical complications necessitating delivery or any condition precluding expectant management, and intrauterine growth retardation (< 10th centile for gestational age).

Microbiological studies

Cervical, vaginal and amniotic fluid samples were obtained for microbiological studies. After Gram staining was performed, the cervicovaginal samples were placed on Stuart media and transport medium (sucrose–phosphate) buffer. Samples were studied for the identification of *C. trachomatis,* urogenital mycoplasmas, *S. agalactiae* and other aerobic and facultative anaerobic bacteria, according to techniques described elsewhere[18–21]. An endocervical white blood cell count was performed using fresh samples.

Amniotic fluid was inoculated into pre-reduced thioglycolate and 2 SP broths. The remaining fluid was transported to the laboratory in a capped plastic syringe immediately after collection. Cultures for aerobic and anaerobic bacteria as well as urogenital mycoplasmas were performed according to methods previously described[22,23].

The diagnosis of bacterial vaginosis was based on vaginal Gram stain according to the method proposed by Nugent and colleagues[24] (evaluation of the frequency of Lactobacillus, *Gardnerella vaginalis,* Bacteroides and Mobiluncus). The presence of these bacterial morphotypes results in a score between 0 and 10. Any value > 6 was considered diagnostic for bacterial vaginosis.

Diagnostic criteria for microbial invasion of the amniotic cavity and cervicovaginal infection

A positive amniotic fluid culture was considered diagnostic for microbial invasion of the amniotic cavity. Cervicovaginal infection was diagnosed in the presence of (1) *C. trachomatis* and/or *N. gonorrhoeae*; (2) urogenital mycoplasmas, aerobic bacteria or facultative anaerobic bacteria (except Lactobacillus), associated with a white blood cell count > 10/field at direct microscopic examination (400 ×); and (3) bacterial vaginosis[25]. We have previously demonstrated that bacterial vaginosis and the isolation of mycoplasmas and other potential pathogens associated with an endocervical white blood cell count of > 10/field in patients with preterm PROM is a risk factor for maternal and neonatal infection morbidity[25].

Randomization and patient management

Patients who met the criteria for inclusion into this study and were willing to participate in the trial were randomized to receive either antibiotics or placebo.

Amniotic fluid was used for microbiological evaluation of the amniotic cavity (cultures for aerobic and anaerobic bacteria as well as mycoplasmas and Gram stain) and a shake test (Clements) for assessment of lung maturity. Results of amniotic fluid Gram stain examination and culture were blinded. However, a positive amniotic fluid culture for *S. agalactiae, Listeria monocytogenes, N. gonorrhoeae* and *H. influenzae* was considered serious enough to warrant notification of the clinician and initiation of antibiotic treatment.

After enrollment, patients were managed expectantly until 35 completed weeks. The pregnancy was terminated if one or more of the following conditions developed: clinical chorioamnionitis, microbial invasion of the amniotic cavity by *Streptococcus agalactiae, Neisseria gonorrhoeae, Haemophilus influenzae* or *Listeria monocytogenes,* fetal distress, and abruptio placentae. Clinical chorioamnionitis was diagnosed following the criteria proposed by Gibbs and associates[26]. The diagnosis required a temperature elevation to 38°C and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, and leukocytosis (> 15 000 cells/mm^3). Puerperal endometritis was defined as a temperature elevation to 38°C or higher on two occasions occurring 4 h apart (excluding the day of delivery), with uterine tenderness, foul-smelling lochia and no other apparent source of infection. Patients with the

diagnosis of chorioamnionitis received intrapartum antibiotics and were delivered. Women with puerperal endometritis were also given antibiotics. Tocolysis and steroids for induction of lung maturity were not used in this study.

Patients with a positive endocervical or vaginal culture for *Streptococcus agalactiae, Neisseria gonorrhoeae* or *Haemophilus influenzae* were treated with penicillin or ampicillin if delivery was imminent, and this was repeated if necessary.

Dosage and administration of antibiotics

Patients randomized to the antibiotic group were prescribed the following antibiotics: clindamycin 600 mg intravenously every 6 h for 48 h and gentamicin 4 mg/kg/day intravenously for 48 h. These agents were followed by clindamycin 300 mg orally every 6 h for 5 days and gentamicin 2 mg/kg/day intramuscularly every 12 h for 5 days. Patients randomized to the control group received corresponding placebos for each drug, both parenterally and orally.

Neonatal management

Pediatricians were aware of the microbiological state of the amniotic fluid and the study treatment received. All neonates under 2000 g received parenteral ampicillin and amikacin after the following examinations were performed: blood cultures, C reactive protein, blood cell count and differential, and peripheral and gastric cultures. Antibiotics were stopped if the clinical examination and/or laboratory tests did not demonstrate the presence of infection. Neonatal sepsis was diagnosed in the presence of a positive culture of blood, urine or cerebrospinal fluid, or clinical signs and laboratory examinations consistent with the diagnosis. Pneumonia was diagnosed in the presence of clinical and radiological findings. The diagnosis of respiratory distress syndrome (RDS) required the presence of respiratory grunting and retracting, an increased oxygen requirement ($FiO_2 > 0.4$), and diagnostic radiographic and laboratory findings in the absence of evidence of other causes of respiratory disease. Necrotizing enterocolitis was diagnosed in the presence of abdominal distension and feeding intolerance for at least 24 h, with clear radiological evidence of intramural air, perforation, meconium plug syndrome or specific surgical or autopsy findings of necrotizing enterocolitis. Intraventricular hemorrhage was diagnosed by ultrasonographic examination of the neonatal head.

Outcome measures

The outcome measures were prolongation of pregnancy, maternal infection-related morbidity, birth weight, neonatal morbidity and admission to the neonatal intensive care unit.

Sample size calculations

These calculations were based on the expected reduction of infection-related maternal morbidity. A study of 320 patients with 160 patients per group was considered to have an 80% power to detect a 40% reduction from a 30% incidence of this outcome in the placebo group ($\alpha = 0.05$). However, the trial was stopped after an interim evaluation demonstrated that patients allocated to the antibiotic group had a better outcome than patients receiving placebo.

Statistical analysis

Comparisons were performed using the χ^2 test, Fisher's exact test, *t*-test or Wilcoxon rank sum test as appropriate. A p value < 0.05 was considered significant. Analysis was performed on an intent-to-treat basis (including all randomized patients).

RESULTS

Study population profile

Eighty eight patients were enrolled in this trial (Figure 1). Eighty-seven patients completed study medications. Seven patients were found to have conditions for exclusion after randomization: four patients in the antibiotic group (one case of uterine malformation, one case with failure to obtain a sample of amniotic fluid, one patient with an intrauterine device and one case of clinical chorioamnionitis that was present but overlooked at admission) and three patients in the placebo group (two cases of lethal fetal malformations and one case with gestational age < 24 weeks, which was corrected after the enrollment of the

patient into the study). All seven patients were managed according to protocol guidelines.

One patient allocated to the placebo group was lost to follow-up. Table 1 displays the characteristics of the study population in both randomization groups. No significant differences in the distribution of various demographic, obstetric and laboratory variables were found between the antibiotic and placebo groups.

Table 1 The patient population according to the study groups. There were no significant differences between the groups

	Antibiotics (*n* = 42)	Placebo (*n* = 46)
Maternal age (years)		
median (SD)	30.5 (6.50)	27.7 (6.62)
range	16–43	15–40
Parity		
primipara	11 (26.2%)	16 (34.8%)
multipara	31 (73.8%)	30 (65.2%)
Gestational age at admission (weeks)		
median (SD)	29.9 (2.46)	29.7 (2.84)
range	24–34	24.4–34
Mode of delivery		
vaginal	22 (52.4%)	24 (53.3%)*
Cesarean section	20 (47.6%)	21 (46.7%)

*One patient lost to follow up

The overall frequency of microbial invasion of the amniotic cavity was 50.6% (44/87) and affected both study groups similarly. All patients with MIAC also had cervicovaginal infection. Cervicovaginal infection without MIAC was present in about 23.9% of patients (10/42 and 11/46 of patients in the antibiotic and placebo groups, respectively). Of patients in both groups, 26.1% had neither MIAC nor cervicovaginal infection.

Table 2 displays the microbiology in patients with MIAC according to study groups. *Ureaplasma urealyticum* was the most common microbial isolate, followed by *Mycoplasma hominis, Streptococcus agalactiae, Gardnerella vaginalis* and *Streptococcus viridans*. No significant differences in the frequency of specific micro-organisms between study groups were observed. Polymicrobial infections were detected in 36.7% (8/22) of patients in the antibiotic group and 50.0% (11/22) of the placebo group. The most frequent microbial isolates from cervix and vagina in the antibiotic and placebo groups were *Ureaplasma urealyticum* 65.6% (21/32) vs. 81.8% (27/33), *Gardnerella vaginalis* 56.3% (18/32) vs. 57.6% (19/33), *Mycoplasma hominis* 25.0% (8/32) vs. 21.2% (7/33) and *Streptococcus agalactiae* 12.5% (4/32) vs. 18.2% (6/33), respectively. Bacterial vaginosis was present in 56.3% (18/32) of patients in the antibiotic group and 45.5% (15/33) in the placebo group.

Table 2 Micro-organisms isolated from the amniotic cavity according to study groups

	Antibiotic group (*n* = 22)		Placebo group (*n* = 22)	
Micro-organism	*n*	%	n	%
Ureaplasma urealyticum	12	54.5	16	72.7
Mycoplasma hominis	3	13.6	3	13.6
Streptococcus agalactiae	2	9.1	2	9.1
Gardnerella vaginalis	3	13.6	3	13.6
Streptococcus viridans	2	9.1	2	10.5
Haemophilus influenzae	2	9.1	2	9.1
Enterococcus sp.	1	4.5	2	9.1
Staphylococcus coagulasa (–)	2	9.1	1	4.5
Peptostreptococcus anaerobius	2	9.1	2	9.1
Peptostreptococcus asaccharolyticus	0	0	1	4.5
Streptococcus pyogenes	0	0	1	4.5
Bacteroides fragilis	1	4.5	0	0
Bacteroides sp.	1	4.5	0	0
Fusobacterium nucleatum	1	4.5	0	0
Candida albicans	1	4.5	0	0

Mixed flora: 36.7% (8/22) in the antibiotic group, 50.0% (11/22) in the placebo group

Table 3 Randomization-to-delivery interval (measured in days) according to microbiological state of the amniotic cavity and lower genital tract

Condition present	Antibiotics (n = 42)	Placebo (n = 45)	p Value
All patients			
mean (SD)	12.1 (10.1)	7.8 (7.8)*	< 0.05
median (range)	10.5 (0–41)	4 (0–32)	
MIAC			
mean (SD)	7.0 (7.7)	3.7 (3.3)	NS
median (range)	4.5 (0–32)	3 (0–14)	
Cervicovaginal infection only			
mean (SD)	20.4 (11.6)	8.7 (7.4)*	< 0.05
median (range)	20 (3–41)	7 (2–23)	
Without MIAC and without cervicovaginal infection			
mean (SD)	14.9 (6.8)	14.2 (9.4)	NS
median (range)	12 (8–29)	10 (2–32)	

*One patient lost to follow-up; MIAC, microbial invasion of the amniotic cavity; NS, not significant

Maternal outcomes

Overall, patients who received antibiotics had a longer randomization-to-delivery interval than patients receiving placebo (median 10.5 days, range 0–41 vs. median 4 days, range 0–32; $p < 0.05$). Similar results were obtained when the analysis was restricted to patients with cervicovaginal infection only (median 20 days, range 3–41 vs. median 7 days, range 2–23; $p < 0.05$). No significant differences were observed in patients with MIAC and in cases without cervicovaginal infection and without MIAC (Table 3).

Maternal infection-related morbidity (clinical chorioamnionitis and puerperal endometritis) was significantly lower in patients who received antibiotics than in patients who received placebo (4.8% (2/42) vs. 28.9% (13/45), respectively, $p < 0.01$, Table 4). In patients with MIAC, the rate of clinical chorioamnionitis was lower in the antibiotic group than in the placebo group (9.1% (2/22) vs. 45.5% (10/22), respectively, $p < 0.01$, Table 5). No significant differences in the rate of clinical chorioamnionitis were observed when the analysis was restricted to patients with cervicovaginal infection only. Patients without either cervicovaginal infection or MIAC did not develop infection-related morbidity (Table 5).

Pregnancy was interrupted in 14.3% of patients who received antibiotics (6/42: four for fetal distress and two for clinical chorioamnionitis) and 33.3% of patients receiving placebo (15/45: 11 for clinical chorioamnionitis, two for fetal distress and two for abruptio placentae). Thirty five weeks of pregnancy was reached by 19.0% (8/42) of patients allocated to receive antibiotics and 6.7% (3/45) of patients who received placebo ($p > 0.05$).

Table 4 Maternal infection-related morbidity according to study groups

	Antibiotics (n = 42)	Placebo* (n = 45)	p Value
Clinical chorioamnionitis	2 (4.8%)	11 (24.4%)	< 0.01
Puerperal endometritis	0	2 (4.4%)	NS
Total	2 (4.8%)	13 (28.9%)	< 0.01

*One patient lost to follow-up; NS, not significant

Neonatal outcomes

No significant differences in the rate of neonatal infection-related morbidity (bronchopneumonia and necrotizing enterocolitis) could be detected (14.3% (6/42) vs. 11.6% (5/43), respectively, $p > 0.05$). Similar results were obtained when the analysis was restricted to newborns whose mothers had MIAC or cervicovaginal infection. The most frequent microbial isolates from amniotic fluid in cases of neonatal

infection were *Streptococcus agalactiae* ($n = 3$), *Mycoplasma hominis* ($n = 2$) and *Haemophilus influenzae* ($n = 1$). No neonatal infection was observed in cases without cervicovaginal infection and without MIAC.

Birth weight was higher in patients of the antibiotic group than in patients of the placebo group (1849 ± 458.4 g vs. 1645 ± 521.4 g, respectively, $p = 0.05$). The rate of neonatal respiratory distress syndrome and admission to the intensive care unit was significantly lower in neonates born to women who received antibiotics than in patients who received placebo (RDS: 9.5% (4/42) vs. 30.2% (13/43), respectively, $p < 0.05$; intensive care admission: 54.8% (23/42) vs. 86.0% (37/43), respectively, $p < 0.01$). No significant differences were observed in the length of stay in the intensive care unit (Table 6).

There were 12 neonatal deaths; seven occurred in patients who had been allocated to the antibiotic group and five in patients who were given placebo. Neonatal infectious morbidity was responsible for five deaths in the antibiotic group and for three deaths in the placebo group. There was one stillbirth in the placebo group.

DISCUSSION

The results of this trial confirm previously published results about the usefulness of antibiotic administration in patients with preterm PROM. Moreover, we have added microbiological information of the cervix, vagina and amniotic cavity to define the group(s) in which this therapy is more likely to have a beneficial effect. The present study demonstrates that antibiotic

Table 5 Maternal infection-related morbidity according to microbiological state of the amniotic cavity and lower genital tract

	Maternal infection-related morbidity		
	Antibiotics ($n = 42$)	Placebo ($n = 45$)	p value
All patients	2/42 (4.8%)	13/45 (28.9%)*	< 0.01
Microbial invasion of the amniotic cavity	2/22 (9.1%)	10/22 (45.5%)	< 0.01
Cervicovaginal infection only	0/10 (0%)	3/10 (30%)*	NS
Without MIAC and without cervicovaginal infection	0/10 (0%)	0/13 (0%)	NS

MIAC, microbial invasion of the amniotic cavity; NS, not significant; *one patient lost to follow-up

Table 6 Neonatal outcome according to study groups

	Antibiotics ($n = 42$)	Placebo* ($n = 43$)	p value
Neonatal weight (g)			
mean (SD)	1849 (458.4)	1645 (521.4)	0.05
median (range)	1825 (980–2820)	1670 (450–2750)	
Admission to intensive care unit	23 (54.8%)	37 (86.0%)	< 0.01
Intensive care stay** (days)			
mean (SD)	6.7 (9.12)	13.2 (19.7)	NS
median (range)	4 (1–42)	7 (1–106)	
Respiratory distress syndrome	4 (9.5%)	13 (30.2%)	< 0.05
Pneumonia	6 (14.3%)	4 (9.3%)	NS
Neonatal sepsis	1 (2.4%)	3 (7.0%)	NS
Intraventricular hemorrhage	3 (7.1%)	7 (16.3%)	NS
Necrotizing enterocolitis	0 (0%)	1 (2.3%)	NS
Neonatal death	7 (16.7%)	5 (11.4%)†	NS

*One patient lost to follow-up, one stillbirth and one neonatal death occurring 10 min after birth (multiple malformations) were excluded; **neonatal deaths were excluded ($n = 12$); †one patient lost to follow-up and one stillbirth were excluded; NS, not significant

administration to women with preterm PROM prolongs the pregnancy and reduces the incidence of maternal infection-related morbidity. Moreover, it decreases the rate of neonatal respiratory distress syndrome and the number of admissions to intensive care units.

Several clinical trials have previously evaluated the usefulness of antibiotic prophylaxis in patients with preterm PROM not in labor (Table 7)[9–16,27–34]. Individual examination of these studies shows important discrepancies. A recently published meta-analysis by Mercer and Arheart[28] indicates that antibiotic administration results in a significant prolongation of the latency period and a reduction in the incidence of delivery within 1 week of admission, clinical chorioamnionitis, postpartum infection, neonatal sepsis, pneumonia and intraventricular hemorrhage. However, no improvement could be demonstrated for other perinatal outcomes such as respiratory distress syndrome, necrotizing enterocolitis and perinatal mortality.

Our results about maternal outcomes are in keeping with previously reported data when analyzed collectively. However, they are at variance with respect to neonatal outcome. Several methodological differences among trials may account for such conflicting results: choice and combination of antibiotics, strategy of analysis, concomitant use of corticosteroids, and sample size limitations. We have chosen clindamycin and gentamicin for their activity on most amniotic fluid micro-organisms, low rate of side-effects and methods of administration. Our study only has a 20–30% power to detect a reduction of 40% (the overall reduction rate from meta-analyzed studies) in the incidence of either neonatal sepsis or intraventricular hemorrhage. Moreover, pediatricians were aware of microbiological cultures obtained from the mother and of treatment arms. Finally, in this study all newborns with birth weight under 2000 g received intravenous antibiotics after birth, management that may decrease the actual rate of clinically evident neonatal sepsis.

On the other hand, the reduction observed in the incidence of respiratory distress syndrome may be explained by the significant prolongation of pregnancy and the corresponding increase in birth weight with the use of antibiotics. In our study, the overall median prolongation of pregnancy was 6.5 days (antibiotic 10.5 days vs. placebo 4 days), while the weighted mean prolongation of pregnancy for previous studies was only 3 days. Moreover, our analysis showed significant differences in birth weight

Table 7 Summary of prospective clinical trials of antimicrobial therapy in patients with preterm premature rupture of membranes (PROM)

Study	*n*	Prolongation of pregnancy	Reduction in maternal infection morbidity	Reduction in neonatal sepsis	Reduction in respiratory distress syndrome	Reduction in necrotizing enterocolitis	Reduction in intraventricular hemorrhage
Gordon and Weingold, 1974[29]	80	—	no	—	—	—	—
Dunlop *et al.*, 1986[30]	48	—	no	no	no	no	no
Amon *et al.*, 1988[13]	82	no	no	yes	—	no	no
Morales *et al.*, 1989[9]	165	—	yes	no	—	no	no
Johnston *et al.*, 1990[10]	85	yes	yes	yes	no	no	yes
McGregor *et al.*, 1991[14]	55	no	no	—	no	no	no
Mercer *et al.*, 1992[15]	220	no	no	no	no	no	no
Christmas *et al.*, 1992[27]	94	yes	no	—	no	no	no
Kurki *et al.*, 1992[31]	101	—	yes	—	—	—	—
Blanco *et al.*, 1993[32]	306	no	—	—	no	—	no
Lockwood *et al.*, 1993[16]	75	yes	no	no	no	—	no
Owen *et al.*, 1993[11]	117	—	yes	no	no	no	no
Ernest and Givner, 1994[12]	148	no	yes	no	no	no	no
Lovett *et al.*, 1996[33]	112	yes	—	yes	yes	no	no
Present study, 1997	88	yes	yes	no	yes	no	no

between treated and non-treated groups (means 1849 g vs. 1645 g, respectively). Such differences were not demonstrated for meta-analyzed studies. In the present study, discrepancies between incidences of respiratory distress syndrome should be attributable only to prolongation of pregnancy, since steroid administration was not part of patient management.

Another potential source of discrepancy between studies is the rate of microbial invasion of the amniotic cavity and cervicovaginal infection. In our study, amniocentesis was performed successfully in 98.9% of patients. Importantly, we found that 50.6% of patients had microbial invasion of the amniotic cavity, the highest prevalence reported in the literature to date. Although we did not have power enough to demonstrate that patients with microbial invasion of the amniotic cavity who received antibiotics had longer admission-to-delivery intervals (because they delivered rapidly after admission), we did observe that antibiotics were associated with a significant reduction in the rate of maternal infectious morbidity in this subset of patients. These findings are in keeping with those reported by Mercer and colleagues[15], and stress the importance of establishing the presence of microbial invasion of the amniotic cavity in patients with preterm PROM.

We found that 74% of patients had cervicovaginal infection, which is potentially responsive to antimicrobial therapy. Indeed, the beneficial effect of antibiotics was particularly marked in these patients. On the other hand, our data show that no cases of microbial invasion of the amniotic cavity occurred in the absence of cervicovaginal infection. Moreover, no differences were found between treated and non-treated groups, in any respect, when patients without cervicovaginal infection were analyzed. These patients had longer latency periods than patients with cervicovaginal infection and did not appear to benefit from additional antibiotic treatment. This is the rationale for proposing that antimicrobial therapy in patients with preterm PROM should be used in all cases unless there is demonstration that cervicovaginal infection is not present. Thus, we have identified a subpopulation of women with preterm PROM which is more likely to benefit from antibiotic administration.

Finally, there is accumulating evidence that aggressive antimicrobial treatment may be the choice in patients with preterm PROM. Previous studies using oral therapy alone have shown prolongation of pregnancy but not benefit regarding maternal or neonatal morbidity[14,15]. Alternatively, studies using prolonged broad-spectrum intravenous treatment have shown that this treatment has a positive impact in the incidence of infectious morbidity in the mother and the newborn[9–13].

To date, a growing body of evidence seems to confirm the benefits of antibiotic administration in patients with preterm PROM. However, active debates still exist regarding fundamental issues such as the route and duration of therapy, the usefulness of concomitant steroids, and the identification of subsets of patients in which antibiotic administration may have a major impact. In this report, we have demonstrated that only patients with evidence of infection of the genital tract benefit from antibiotic therapy. Further investigation directed to the development of rapid tests in the cervix and vagina may constitute a practical approach to select such cases.

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