Archives of Gynecology and Obstetrics (2019) 300:569–573
https://doi.org/10.1007/s00404-019-05221-w

MATERNAL-FETAL MEDICINE

Macrolide antibiotics roxithromycin vs. azithromycin for preterm premature rupture of membranes: a retrospective comparison

Hanoch Schreiber[1,3] · Pnina Shitrit[2,3] · Gili Man-El[1,3] · Offra Engel[1,3] · Arie Berkovitz[1,3] · Tal Biron-Shental[1,3]

Received: 10 March 2019 / Accepted: 15 June 2019 / Published online: 22 June 2019

Abstract

Purpose Prophylactic antibiotics to prolong latency and reduce the risk of neonatal and maternal infections are used for preterm premature rupture of membranes. This study compared outcomes between two macrolides: roxithromycin given twice a day for a week and azithromycin, given as a single dose, which is more convenient.

Methods Two local protocols were retrospectively compared: roxithromycin and ampicillin from July 2005 to May 2016, and azithromycin and ampicillin from May 2016 to May 2018. Inclusion criteria were singleton pregnancy, at 24–34 weeks of gestation upon admission with preterm premature rupture of membranes. Primary outcome was length of the latency period, defined as time from first antibiotic dose to 34 + 0 weeks, or spontaneous or indicated delivery prior to 34 + 0 weeks. Secondary outcomes were rates of chorioamnionitis, delivery mode, birth weight and Apgar scores.

Results A total of 207 women met inclusion criteria, of whom, 173 received penicillin and roxithromycin and 34 received penicillin and azithromycin. Baseline characteristics were similar between groups. The latent period was longer in the azithromycin group than in the roxithromycin group (14.09 ± 14.2 days and 7.87 ± 10.2 days, respectively, $P = 0.003$). Rates of chorioamnionitis, cesarean deliveries, Apgar scores and birth weights were similar between the groups.

Conclusions Azithromycin compared to roxithromycin results in a longer latency period in the setting of preterm premature rupture of membranes at 24–34 weeks of gestation. Given its more convenient regimen and our results, it seems justified to use azithromycin as the first-line treatment for patients with preterm premature rupture of membranes.

Keywords Azithromycin · Latency period · Preterm premature rupture of membranes · Prophylactic antibiotics · Roxithromycin

Introduction

Preterm premature rupture of the membranes (PPROM) occurs in 3% of pregnancies [1]. Most women with PPROM deliver within a week from the onset of membrane rupture [2, 3].

Many factors may be involved in the pathophysiology of PPROM. Infection, inflammation or mechanical stress that lead to membrane dysfunction or bleeding can initiate a process that leads to rupture of the membranes [4–6]. In the case of PPROM from 24 to 34 weeks, to reduce the complications of prematurity, pregnancy is continued as long as there are no signs of chorioamnionitis [7].

Routine prescription of antibiotics for women with preterm rupture of the membranes is associated with prolonged gestation and with decreased risk of neonatal and maternal infections [8–10]. There is insufficient information to determine the optimal antibiotic regimen. Based on the available data, treatment with a 7-day course of therapy with a combination of intravenous ampicillin and erythromycin, followed by oral amoxicillin and erythromycin is recommended while expectantly managing women with PPROM before 34 + 0 weeks of gestation [7].

Hanoch Schreiber and Pnina Shitrit contributed equally.

✉ Hanoch Schreiber
hanochsc@gmail.com

[1] Department of Obstetrics and Gynecology, Meir Medical Center, 59 Tchernichovsky St, 44281 Kfar Saba, Israel

[2] Infectious Disease Unit, Meir Medical Center, Kfar Saba, Israel

[3] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Other macrolide antibiotics such as azithromycin and roxithromycin are also given with penicillin based on their activity against the major pelvic pathogens. Macrolide antibiotics act by binding to the 50 S ribosomal subunits of susceptible bacteria, thereby suppressing bacterial protein synthesis. These drugs are bacteriostatic at low concentrations and bactericidal at high concentrations. Azithromycin is an azalide, which is a subclass of the macrolides. It is derived from erythromycin; however, it differs chemically because a methyl-substituted nitrogen atom is incorporated into the lactone ring [11, 12]. The current study compared the use of ampicillin and azithromycin to a regimen of ampicillin and roxithromycin. The primary outcome was the latency period, defined as time from first antibiotic dose to 34 + 0 weeks or spontaneous or indicated delivery prior to 34 + 0 weeks. Secondary outcomes were rates of chorioamnionitis, mode of delivery, birth weight and Apgar scores.

Materials and methods

This retrospective, cohort analysis included women admitted with a diagnosis of PPROM from July 2005 to May 2018 to a university-affiliated medical center. The study was approved by the Meir Medical Center Ethics Committee, approval number 0075-18-MMC, March 2018. Informed consent was not required.

According to departmental protocol, all women with PPROM from July 2005 to May 2016 were treated with intravenous ampicillin (2 g every 6 h) and oral roxithromycin (150 mg every 12 h) for 48 h, followed by oral amoxicillin and roxithromycin for another 5 days. In May 2016, the local protocol was changed to a one-time dose of 1 g oral azithromycin instead of 7 days of roxithromycin, for ease of administration.

Inclusion criteria were a singleton pregnancy with PPROM at 24–34 weeks of gestation. The data were analyzed on an intention-to-treat basis. Women who did not complete the entire course of therapy were not excluded.

Exclusion criteria were pregnancies at less than 24 or more than 34 weeks gestation, patients admitted in preterm labor with concomitant rupture of membranes, multiple gestations and those carrying a fetus with lethal anomalies.

Data were retrieved from the comprehensive electronic medical records of labor and delivery. All records with a diagnosis of PPROM were reviewed. Demographic parameters, antibiotic information (regimen, timing of administration) and obstetrical course (time and route of delivery, and the presence or absence of chorioamnionitis) were abstracted for each patient. Chorioamnionitis was determined based on clinical diagnosis and placental pathology.

The primary study outcome was the duration of latency, defined as time from first antibiotic dose to 34 + 0 weeks gestation, or spontaneous or indicated delivery prior to 34 + 0 weeks. Secondary outcomes were rates of chorioamnionitis, mode of delivery, birth weight and Apgar scores.

The data of all patients who met the inclusion criteria and delivered in our institution were analyzed. Therefore, we conducted a post hoc power analysis that revealed over 95% power with an alpha error of 0.05 for the size of the study population.

Statistical methods

Data are described as number and percentage for nominal variables and mean and standard deviation for continuous parameters. Chi-squared or Fisher's Exact test was conducted to find differences between roxithromycin and azithromycin in nonmetric data. The continuous variables were checked for normality with Shapiro–Wilk test. Those with normal distribution were analyzed with *t* test; others with Mann–Whitney non-parametric test. Kaplan–Meier analysis was used to estimate the time to delivery between the two groups of medications. $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS-25 software (IBM, Armonk, NY, USA).

Results

From July 2005 through May 2018, 207 women met the study inclusion criteria. They were identified based on documentation of PPROM in the medical records. Baseline characteristics and demographics were similar between women in the two protocol groups, except the rate of previous cesarean delivery was higher in the azithromycin group. Patients were treated with antenatal corticosteroids for lung maturation. The groups were similar regarding receipt of antenatal corticosteroids for lung maturation and treatment with tocolytics (Table 1). The latency period was significantly longer in women who received ampicillin and azithromycin as compared to those who received ampicillin and roxithromycin (14.09 ± 14.2 days vs. 7.87 ± 10.2 days, $P = 0.003$; Table 2).

The difference in latency between azithromycin and roxithromycin was maintained even after women who gave birth 24 h after rupture of membranes were excluded. In this case, the latency was 15.4 ± 14.2 and 9.6 ± 10.6 days, respectively ($P = 0.011$). After excluding those who delivered 48 h after rupture of membranes, latency periods were 17.5 ± 14.1 days and 11.0 ± 10.9 days, respectively ($P = 0.009$). The latency interval from first antibiotic dose to 34 + 0 weeks of gestation or delivery before 34 + 0 weeks is depicted in Fig. 1. Based on Mantel–Cox survival analysis, the difference was $P = 0.011$.

There was no difference in the rate of clinical chorioamnionitis, Apgar scores, primary cesarean deliveries or live

Table 1 Baseline population characteristics

Parameter	Azithromycin ($N=34$)	Roxithromycin ($N=173$)	P value
Average age (years) ± SD	33.3 ± 5.0	32.02 ± 6.0	0.237
Gravidity	3.15	2.72	0.224
Parity	2.41	2.12	0.268
Gestational age at ROM (weeks)	30 + 2	30 + 1	0.652
Previous cesarean section, *N* (%)	10 (29.4)	20 (11.6)	0.007
Group B Strep positive, *N* (%)	2 (5.9)	16 (9.2)	0.47
Antenatal corticosteroids, *N* (%)	34 (100)	165 (95.3)	0.311
Tocolytic therapy, *N* (%)	4 (11.8)	37 (21.4)	0.193

ROM rupture of membranes

births. Placental culture results were available for 88 cases, and the rates of culture-confirmed chorioamnionitis were similar between the groups: 4/15 (26%) treated with azithromycin and 29/73 (39%) with roxithromycin ($P=0.34$). There was no difference in neonatal birth weights, adjusted for gestational age at delivery. The duration of NICU stay was related to the gestational age at delivery and not to the type of antibiotics. No severe adverse drug reactions with azithromycin or roxithromycin were documented in any of the medical records.

Discussion

This retrospective study of two antibiotic regimens for the treatment of preterm, premature rupture of membranes revealed an advantage of azithromycin over roxithromycin in prolonging the latency period between membrane rupture and delivery.

We calculated latency up to 34 weeks of gestation because there is a consensus regarding the importance of conservative treatment until this time. The complications of prematurity prior to 34 weeks are significant enough to justify all efforts that might increase the time from membrane rupture to delivery. Beyond 34 weeks, some data support conservative management but there is still no consensus. Therefore, the current study focused on latency until 34 weeks only.

The average duration of the latency period based on previously published data is 4–12 days [13, 14]. The results presented here are within the same time frame, which strengthens its applicability to other populations.

The reported rate of chorioamnionitis among patients with PPROM is 12–27.7% [13, 15]. The rate of chorioamnionitis in our cohort was similar in both treatment groups, at about 13%, comparable to previous studies.

A 7-day course of therapy with a combination of intravenous ampicillin and erythromycin, followed by oral amoxicillin and erythromycin is recommended during expectant management of women with PPROM who are at less than 34 + 0 weeks of gestation but the optimal antibiotic regimen is unclear [7].

Although azithromycin has a broader spectrum of activity compared to erythromycin [16], one retrospective study

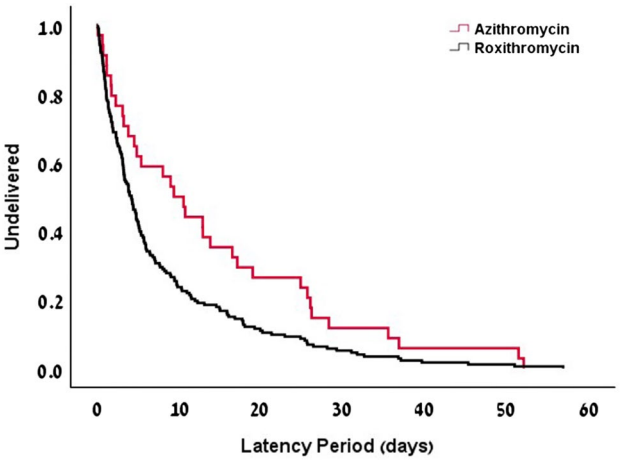

Fig. 1 Interval to delivery. The latency interval from first antibiotic dose to 34 + 0 weeks of gestation or delivery before 34 + 0 weeks was plotted and analyzed as a Kaplan–Meier curve. The difference was calculated as $P=0.011$ using Mantel–Cox survival analysis

Table 2 Study outcomes

Outcome	Azithromycin ($N=34$)	Roxithromycin ($N=173$)	P value
Primary			
Latency (days)	14.09 ± 14.2	7.87 ± 10.2	0.003
Secondary			
Clinical chorioamnionitis, *N* (%)	9 (26.5)	23 (13.3)	0.069
Primary cesarean delivery (%)	13 (38)	56 (32)	0.106
Birth weight (g)	1863.4 ± 480.7	1695.1 ± 507.1	0.093
Live birth, *N* (%)	34 (100)	173 (100)	NA
APGAR score ≤ 7 at 1 min, *N* (%)	7 (20.6)	39 (22.5)	0.688
APGAR score ≤ 7 at 5 min, *N* (%)	0	10 (5.7)	0.216

found no difference in the duration of latency or other outcomes between azithromycin and erythromycin [17].

No studies directly compare the spectrum of activity of azithromycin vs. roxithromycin, and they are considered to have similar coverage. However, the pharmacokinetic properties of the two preparations differ. The half-life of azithromycin is approximately 68 h, while the half-life of roxithromycin ranges from 8 to 13 h [18]. The dosing regimens commonly used for PPROM are also different: 7 days for roxithromycin compared to a single dose of azithromycin, which contributes to their different pharmacokinetic profiles.

A possible mechanism explaining the different efficacies of these two antibiotics in prolonging the latency period may be related to their pharmacokinetic properties. The effectiveness of azithromycin depends on its concentration in the tissue. A high initial dose of azithromycin leads to high concentrations of the drug early in the course of PPROM. Its long half-life means that it remains at therapeutic concentrations for an extended time [11], which may be the key to prolonging the latency period.

This study had some limitations. The data were retrieved from the comprehensive electronic database of the hospital delivery records and we might have failed to identify some women with PPROM. However, each record with a diagnosis fitting rupture of membranes between weeks 24 and 34 was examined individually. In addition, fewer women were treated with azithromycin than with roxithromycin due to the time periods of the two protocols. This might cause a bias that could be overcome by conducting a randomized, controlled trial.

Conclusion

The results of this study indicate that azithromycin results in a longer latency period than roxithromycin does. Higher antibiotic doses administered early in the course of PROM may lead to greater drug delivery, which may be the key to prolonging the latency period. Further studies are indicated to form a more solid conclusion, but due to the ease of administration of azithromycin and these results, it seems logical to use it as the first-line treatment for preterm PROM patients.

Acknowledgements The authors thank Nava Jelin, MS for data analysis, and Faye Schreiber, MS for editing the manuscript. They are employees of Meir Medical Center.

Author contribution HS: study conception and design, and manuscript revisions. PS: data collection, data analysis and interpretation, and manuscript writing. GM-E: data collection, data analysis and interpretation, and manuscript writing. OE: data collection, data analysis and interpretation, and manuscript writing. AB: data analysis and interpretation, and manuscript writing. TB-S: study conception and design, and data interpretation.

Funding This study was not funded.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Meir Medical Center Ethics Committee in March 2018, approval number 0075-18-MMC. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not required.

References

1. Mercer BM (2005) Preterm premature rupture of the membranes: current approaches to evaluation and management. Obstet Gynecol Clin N Am 32:411–428
2. Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Ramsey RD et al (1997) Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. JAMA 278:989–995
3. Melamed N, Hadar E, Ben-Haroush A, Kaplan B, Yogev Y (2009) Factors affecting the duration of the latency period in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 22(11):1051–1056
4. Averbuch B, Mazor M, Shoham-Vardi I, Chaim W, Vardi H, Horowitz S, Shuster M (1995) Intra-uterine infection in women with preterm premature rupture of membranes: maternal and neonatal characteristics. Eur J Obstet Gynecol Reprod Biol 62:25–29
5. Rocha FG, Slavin TP, Li D, Tiirikainen MI, Bryant-Greenwood GD (2013) Genetic associations of relaxin: preterm birth and premature rupture of fetal membranes. Am J Obstet Gynecol 209(258):e1–8
6. French JI, McGregor JA (1996) The pathobiology of premature rupture of membranes. Semin Perinatol 20:344–368
7. Practice Bulletin No. 172: Premature rupture of membranes (2016) American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Obstet Gynecol 128:e165–e177. https://doi.org/10.1097/AOG.0000000000001712
8. Kenyon S, Boulvain M, Neilson JP (2013) Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 12:CD001058. https://doi.org/10.1002/14651858.CD001058.pub3
9. Daskalakis G, Goya M, Pergialiotis V et al (2019) Prevention of spontaneous preterm birth. Arch Gynecol Obstet 299:1261–1273. https://doi.org/10.1007/s00404-019-05095-y
10. Park JW, Park KH, Kook SY et al (2019) Immune biomarkers in maternal plasma to identify histologic chorioamnionitis in women with preterm labor. Arch Gynecol Obstet 299:725–732. https://doi.org/10.1007/s00404-019-05061-8
11. Blumer JL (2005) Evolution of a new drug formulation: the rationale for high-dose, short-course therapy with azithromycin. Int J Antimicrob Agents 26(Suppl 3):S143–S147
12. Yonath A (2005) Antibiotics targeting ribosomes: resistance, selectivity, synergism, and cellular regulation. Annu Rev Biochem 74:649–679
13. Yudin MH, van Schalkwyk J, Van Eyk N (2017) No. 233-Antibiotic therapy in preterm premature rupture of the membranes.

J Obstet Gynaecol Can 39:e207–e212. https://doi.org/10.1016/j.jogc.2017.06.003
14. Dale PO, Tanbo T, Bendvold E, Moe N (1989) Duration of the latency period in preterm premature rupture of the membranes. Maternal and neonatal consequences of expectant management. Eur J Obstet Gynecol Reprod Biol 30:257–262
15. Goya M, Bernabeu A, García N, Plata J, Gonzalez F, Merced C, Llurba E, Suy A, Casellas M, Carreras E, Cabero L (2013) Premature rupture of membranes before 34 weeks managed expectantly: maternal and perinatal outcomes in singletons. J Matern Neonatal Med. 26:290–293
16. Zuckerman JM (2004) Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. Infect Dis Clin N Am 18:621–649
17. Pierson RC, Gordon SS, Haas DM (2014) A retrospective comparison of antibiotic regimens for preterm premature rupture of membranes. Obstet Gynecol 124:515–519
18. Puri SK, Lassman HB (1987) Roxithromycin: a pharmacokinetic review of a macrolide. J Antimicrob Chemother 20(suppl B):89–100