IMPACT OF AZITHROMYCIN ON PREGNANCY PROLONGATION IN WOMEN AT RISK OF PRETERM LABOR: A TIME-TO-EVENT ANALYSIS

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ABSTRACT

Background
Since 2006, the empiric use of azithromycin in women at risk of premature birth has become prevalent in our institution without any evidence of its efficacy. Although antibiotics can prolong pregnancy in preterm prolonged rupture of membranes, no published data are available for women with intact membranes.

Objectives
To describe the purpose of adding azithromycin to the usual treatments (cerclage, tocolysis, rest, etc.) to prolong pregnancy in women with intact membranes who are at risk of or already in preterm labour.

Methods
A retrospective observational cohort study was done at a Mother-Child University Hospital Centre. Patients admitted to obstetric ward who received azithromycin between January 1st, 2006 and August 1st, 2010 were included. A total of 127 exposed women were matched to 127 controls through medical records and pharmacy software. A time-to-event analysis was done to compare gestational age at the time of the recorded composite event (delivery, or rupture of membranes, or second intervention to prolong pregnancy). To compare proportions of composite event at different time points, χ^2 tests were used.

Results
Patients who received azithromycin had a more severe condition at presentation. Once adjusted for confounding factors, prolongation of pregnancy (HR =1.049; CI 95%: 0.774–1.421 [p=0.758]) and gestational age at the event (HR=1.200; CI 95%: 0.894–1.609 [p=0.225]) did not differ between the groups. The proportions of women with an event ≥7 days post-diagnosis or ≥37 gestational weeks were similar.

Conclusions
Azithromycin was added to medical therapy in a more at-risk population and no clear benefit was measured.

Key Words: *antibiotic, pregnancy, azithromycin, premature birth, preterm birth, preterm labour*

Preterm birth is the main cause of perinatal morbidity and mortality around the world and its incidence continues to increase in North America.[1,2] In Quebec, the rate of premature births, defined as occurring before 37 completed weeks gestation, was 7.4% in 2007.[3] Perinatal complications are more frequent in neonates born before the 34th week of gestation.[4,5] Risk factors for preterm labour include premature rupture of membranes, short cervix, infection, previous preterm labour, multiple pregnancy, maternal age > 35 years, African-American descent, and smoking.[6–8]

Recently, amniotic fluid sludge, defined as intra-amniotic aggregates seen at the ultrasound, has been identified as a risk factor of preterm labour[9] and is thought to be a surrogate marker of amniotic fluid inflammation. Amniotic sludge is observed in 10–40% of all preterm births.[10–12] Moreover, studies have shown a significant link between cervix shortening, microbial invasion, and imminent birth.[13]

Several interventions may lengthen pregnancy in women at risk of preterm delivery including cervical cerclage, tocolytics, progesterone, and infection treatment or prophylaxis.[14–19] Antimicrobials, mainly macrolides, have been used to eradicate vaginal flora colonizers (*Mycoplasma hominis*, *Ureaplasma urealyticum*) in order to prevent amniotic fluid infection and subsequent inflammation cascade, thereby lowering the risk of preterm labour.[20,21]

Since 2006, the empiric use of azithromycin in women at risk of premature birth has become prevalent in our institution without any evidence of its efficacy. Although, antibiotics can prolong pregnancy in preterm prolonged rupture of membranes (PPROM), no published data is available for women with intact membranes.[22] The purpose of this observational study is to describe the purpose of adding azithromycin to usual treatments to prolong pregnancy in women with intact membranes at risk of or in preterm labour.

The secondary objectives are to evaluate the impact of azithromycin on gestational age at the time of the recorded composite event (delivery, or rupture of membranes, or second intervention to prolong pregnancy) and proportion of prolonged pregnancies ≥7 days and composite events ≥34 and ≥37 weeks.

METHODS

This is a retrospective observational cohort study. Using the pharmacy software, we retrieved a list of all patients admitted on the obstetrics ward who received azithromycin between January 1st, 2006 and August 1st, 2010. The control group was identified using medical records. Each azithromycin patient was matched for gestational age at admission (±1 week). Inclusion criteria were: <34 weeks of gestation, hospitalized for risk of preterm labour, threat of preterm labour, or preterm labour itself. Threat of preterm labour and preterm labour had to be diagnosis cited in the medical record by the physician.

Women at risk of preterm labour had to have one of the following conditions cited in their record: sludge, short cervix, cerclage, or bulging membranes. Exclusion criteria were: antibiotics use within 14 days prior to admission (except for pericerclage prophylaxis, or *streptococcus B* prophylaxis); PPROM; and fetal extraction required <37 weeks.

Main outcome was the number of days between diagnosis and composite event, defined as delivery or rupture of membranes or 2nd intervention aimed at prolonging pregnancy (such as cerclage or tocolysis) or censure (maternal death or transfer). Gestational age at the time of composite event was estimated with ultrasound or, if unavailable, calculated with the date of last menstrual period.

The following information was collected from the medication administration form: azithromycin dosage, duration of treatment, cumulative dose, and date of first dose. Subgroup analyses were performed for the following subgroups: gestational age <28 weeks at diagnosis, sludge, emergency or planned cerclage, preterm labor and short cervix (<25 mm at <34th week). All data were compiled using a standardized data collection sheet. Confounders that were considered for inclusion were gestational age at admission, maternal weight at time of first pregnancy follow-up, maternal age at admission, and risk factors that influenced severity of the condition (preterm labour, chorioamnionitis, short cervix, sludge, bulging membranes, cerclage, multiple pregnancy, diabetes, hypertension, anemia, intrauterine growth retardation, poly/oligohydramnios and pre-eclampsia), previous premature birth or preterm labour, ethnic origin, smoking, alcohol use, substance abuse, and administration of tocolytics, progesterone or other antibiotics. Risk factors were identified using published evidence. Data collection was performed by the authors.

Statistical analyses

Statistical analyses were performed using IBM® SPSS® Statistics® (SPSS version 19, Chicago, IL, USA). Results were compared with Student's *t* test for means and χ^2 for proportions. Non parametric tests for median differences were carried out if continuous variables did not follow a normal distribution. For the primary objective, a time-to-event analysis with Kaplan-Meier curves and log-rank tests were carried out. Time 0 was defined as the day of diagnosis, censoring as death or transfer, and composite event as delivery or rupture of membranes or initiation of a 2nd intervention to prolong pregnancy.

Multivariable Cox's proportional hazards regression model with backward elimination of

non-significant covariates (p>0.15) was carried out. A similar model was carried out for gestational age at the time of the composite event, with identical definitions of parameters. α thresholds were 0.05 and 95% confidence levels were calculated for primary and secondary objectives.

Adjustments for covariables were made using a step-down multivariable logistic regression. According to Rajaei et al., the use of erythromycin in pregnant women with preterm labour and intact membranes prolongs pregnancy by 33.33±18.36 days versus 26.88±13.9 days for placebo, a 6.45

TABLE 1 Demographic and medical data

	Controls *n* (%)	Azithromycin *n* (%)	*p*
Total	127	127	--
Demographic			
Mean Age	29.8 yrs	29.0 yrs	0.253
Pre-pregnancy weight (kg)	65.2	67.9	0.312
Smoking	20 (15.7)	21 (16.5)	0.865
Alcohol	5 (3.9)	5 (3.9)	1.000
Drug use	7 (5.5)	4 (3.1)	0.355
Present Pregnancy			
Mean gestational age at admission (weeks)	$23^{5/7}$	$23^{3/7}$	0.663
Type of pregnancy: Singleton Twin Triplets	 111 (87.4) 13 (10.2) 3 (2.4)	 107 (84.3) 16 (12.6) 4 (3.1)	0.769
Preterm labour	**38 (30.0)**	**26 (20.5)**	**0.083**
Threatened preterm labour	43 (33.9)	46 (35.4)	0.693
Risk factors for preterm labour	46 (35.4)	55 (43.3)	0.249
• **Chorioamnionitis**	**2 (1.6)**	**15 (11.8)**	**0.001**
• **Short cervix***	**54 (42.5)**	**79 (62.2)**	**0.002**
• **Amniotic sludge**	**6 (4.7)**	**48 (37.8)**	**<0.001**
• **Bulging membranes**	**30 (23.6)**	**53 (41.7)**	**0.002**
• **Cerclage** ○ **Emergency** ○ **Planned**	**29 (22.8)** **12** **17**	**44 (34.7)** **30** **14**	**0.010**
• Intra-uterine growth retardation	1 (0.8)	2 (1.6)	0.561
• **Polyhydramnios**	**1 (0.8)**	**5 (3.9)**	**0.098**
• Oligohydramnios	5 (3.9)	2 (1.6)	0.250
Progesterone treatment	**31(24.4)**	**45 (35.4)**	**0.055**
Administration of tocolytics**	51 (40.2)	55 (43.3)	0.611
Administration of betamethasone***	60 (47.2)	71 (55.9)	0.167
Other antibiotics during hospitalization**	**20 (15.8)**	**40 (31.5)**	**0.003**

Characteristics in bold were added to multivariable statistical models.
* = short cervix: length ¡Ü 25 mm in single pregnancies and ¡Ü 15 mm in multiple pregnancies; ** = tocolytics: MgSO4, nifedipine and/or indomethacin; *** = for fetal pulmonary maturation; **** = antibiotics other than those used for the treatment of intrapartum group B streptococcus or per cerclage.
Ethnicity was equally distributed. Proportions with specific medical histories (diabetes, hypertension, obesity, dyslipidemia, asthma, human immunodeficiency virus, pelvic or sexually transmitted infections, depression or anxiety, hypothyroidism, anemia, inflammatory bowel disease, heart or renal disease) were not statistically different. Past obstetrical issues (preterm delivery or labour, PPROM, cerclage, pre-eclampsia, nullipara, gravida, parity, term, abortion) were evenly distributed between the groups.

daysdifference.[23] With posteriori calculations, for a bilateral log-rank test with α = 0.05, our power to detect a similar significant difference was 62% (β=0.38) with a sample size of *n*=127 per group.

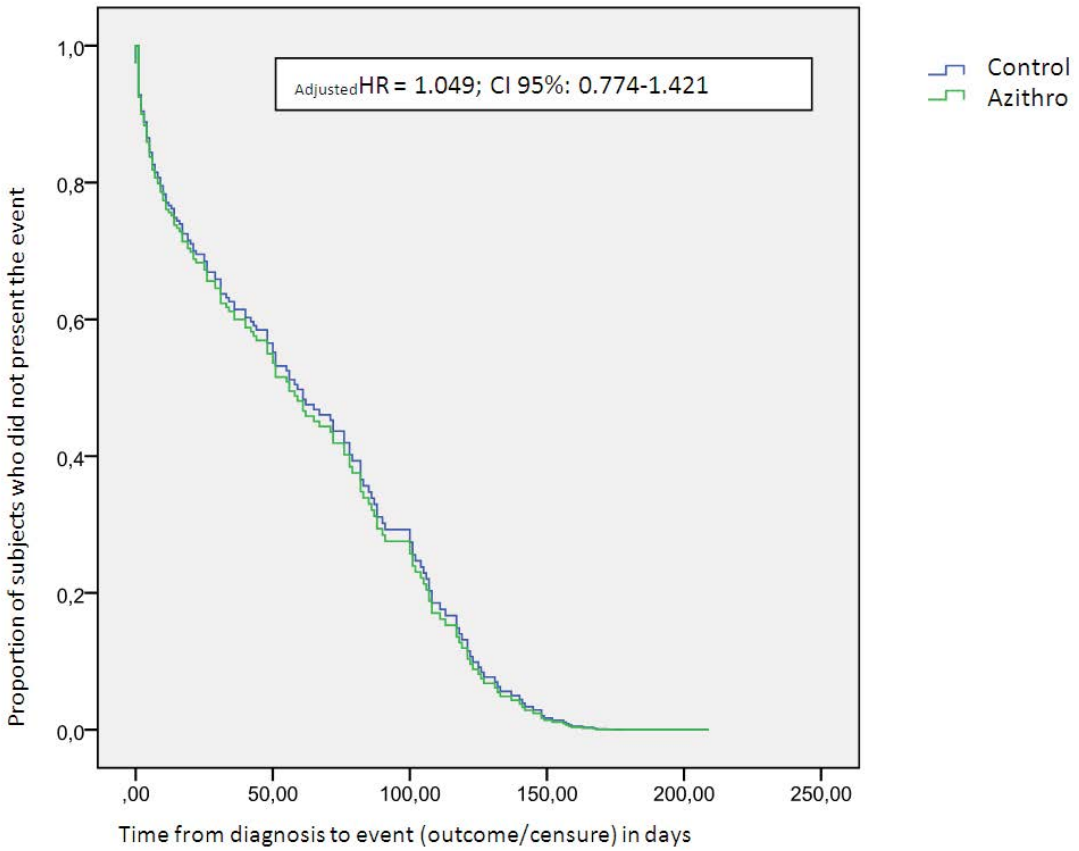
The study was approved by Ethics and Research Committee and the Direction of Medical and University Affairs of Sainte-Justine UHC. No informed consent was required given the retrospective nature of the study.

RESULTS

Out of 183 pregnancies in the azithromycin group, 127 met the inclusion criteria and were matched with 127 controls (316 charts were reviewed for inclusion criteria). Demographics and current or previous obstetrical issues did not differ between groups (Table 1) except for severity of condition at admission. Patients in the azithromycin group had significantly more risk factors for preterm birth: chorioamnionitis, short cervix, sludge, bulging membranes, cerclage, or polyhydramnios). There were more pregnancies for which other antibiotics (mainly for urogenital infections or *streptococcus B* prophylaxis) and progesterone were prescribed in the azithromycin group.

When drafting the protocol, it was estimated that administration of azithromycin depended more on the physician than on the severity of the condition. During preliminary analyses, it was noted that this was not the case, since the exposed subjects generally had a more severe presentation. This confounding factor, as well as the previously mentioned covariables, was taken into account when adjusting the results to

FIG. 1 Time-to-event curve - primary outcome. This figure represents a Cox regression on the primary outcome, i.e., the proportion of subjects who did not present the composite event over time starting from diagnosis. Composite event = delivery or rupture of membranes or 2nd intervention to prolong pregnancy. Censure = death or transfer.



minimize confounding bias. Covariables were added to multiple regressions, except for chorioamnionitis and polyhydramnios, as the disparity in these group sizes and their small sample jeopardized the model's stability.

Main outcome

Delivery date was known for 97 controls and 100 treated patients; 30 controls and 27 pregnancies on azithromycin had to be censured. The median number of days to delivery for controls was 76.0 and 40.0 for azithromycin patients. A comparison of the Kaplan-Meier curves in the 2 groups with regards to time-to-event does not show a statistically significant difference: log-rank (Mantel-Cox)=3.662; p=0.056 (Figure 1). For the Cox regression, the following covariables showed a significant effect: preterm labour, cerclage and bulging membranes. Once adjusted, the results did not show a significant difference between treatment groups: HR =1.049; CI 95%: 0.774–1.421 (p=0.758).

Secondary outcomes

Median gestational age at the composite event in the control group was 36 5/7 weeks and 32 0/7 weeks with azithromycin. Kaplan-Meier curves of the two groups for gestational age at the time of the composite event show a statistically significant difference: log-rank (Mantel-Cox)=4.120; p=0.042 (Figure 2). For the Cox regression, the following covariables demonstrated a significant effect: preterm labour, bulging membranes, and polyhydramnios. Once the results were adjusted, treatment group had no significant influence: HR=1.200; CI 95%: 0.894–1.609 (p=0.225).

FIG. 2 – Time-to-event curve - gestational age at the composite event. This figure represents a Cox regression of the proportion of subjects who did not present the composite event versus the gestational age. Composite event = delivery or rupture of membranes or 2nd intervention to prolong pregnancy. Censure = death or transfer.

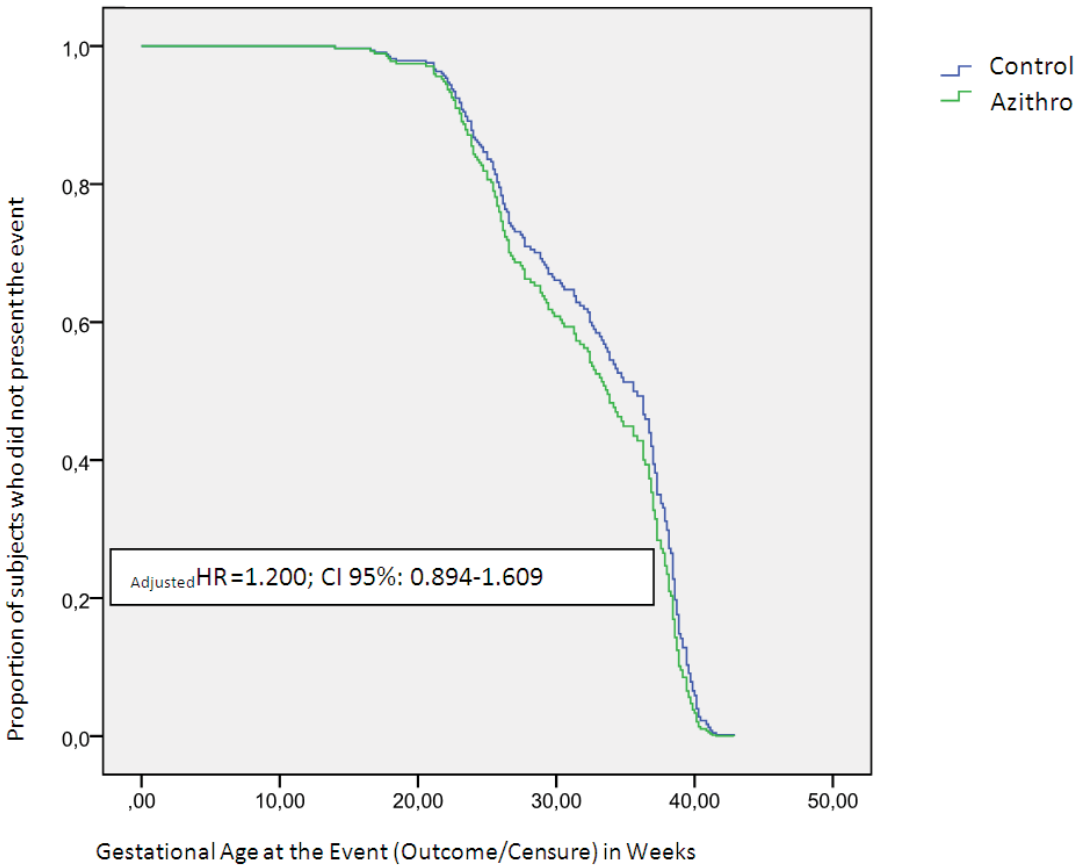


TABLE 2 Secondary outcomes (logistic regressions).

	Composite Event ≥ 7 Days			Composite Event ≥ 37 Weeks			Composite Event ≥ 34 Weeks		
Variable	OR	CI 95%	*p*	OR	CI 95%	*p*	OR	CI 95%	*p*
Treatment Group	1.513	0.738 – 3.100	0.258	0.714	0.368 – 1.386	0.320	**0.520**	**0.291 – 0.927**	**0.027**
Preterm Labour	0.589	0.288 – 1.204	0.146	**0.345**	**0.136 – 0.872**	**0.025**	0.537	0.256 – 1.128	0.100
Short Cervix	--	--	--	**0.417**	**0.211 – 0.825**	**0.012**	--	--	--
Sludge	2.103	0.794 – 5.564	0.135	--	--	--	--	--	--
Bulging Membranes	**0.226**	**0.114 – 0.445**	**<0.001**	**0.322**	**0.142 – 0.731**	**0.007**	**0.272**	**0.136 – 0.547**	**<0.001**
Type of Cerclage:			**0.076**			**0.085**			**0.051**
Cerclage (Emergency)	1.806	0.673 – 4.850	0.241	1.836	0.795 – 4.239	0.155	1.715	0.785 – 3.747	0.176
Cerclage (Planned)	**8.606**	**1.090 – 67.968**	**0.041**	**2.495**	**1.010 – 6.161**	**0.047**	**2.775**	**1.157 – 6.656**	**0.022**
Progesterone Treatment	**2.733**	**1.200 – 6.226**	**0.017**	--	--	--	--	--	--
Polyhydramnios	--	--	--	4.365	0.660 – 28.875	0.126	--	--	--

-- = variables not included in the model given its non significant confounding effect.

In the control group, 87 pregnancies (68.5%) were prolonged ≥7 days post-diagnosis and 97 (76.4%) on azithromycin; not statistically different (OR=1.972; *p*=0.16) (Table 2). After logistic regression, the odds of prolonging the pregnancy ≥7 days did not significantly differ between groups (OR=1.513; CI 95%: 0.738–3.100; [ᵖ=0.258]). In the control group, 40 composite events (31.5%) occurred at ≥37 weeks and 28 (22.0%) in patients on azithromycin. These proportions were not statistically different (OR=0.346; *p*=0.089). After logistic regression, the odds of the composite event happening at ≥37 weeks were similar in the two groups (OR=0.714; CI 95%: 0.368–1.386 [*p*=0.320]). In the controls, 58 composite events (45.7%) occurred at ≥34 weeks and 38 (29.9%) on azithromycin; this was statistically different (OR=0.149; *p*=0.010). After logistic regression, odds of presenting the composite event at ≥34 weeks in the control group were twice as high as in the azithromycin group (OR=0.520; CI 95%: 0.291–0.927 [*p*=0.027]).

Median initial and maintenance azithromycin

TABLE 3 Descriptive data on azithromycin treatment.

Characteristics	**Median**	**Min. – Max.**	***n* per value or category (%)**
Dose (mg/day)	250	0 - 1000	0 mg: 21 (16) ; 250 mg: 73 (58) ; 500 mg: 32 (25) ; 1,000 mg: 1 (1)
Initial dose (mg)	500	0 – 2,000	0 mg: 21 (16.5); 250 mg: 3 (2) ; 500 mg: 81 (64); 1,000 mg: 21 (16.5); 2,000 mg: 1 (1)
Treatment duration (days)	4	0 - 18	0 – 5 days: 79 (62); 6 – 10 days: 44 (35); 10 or + days: 4 (3)
Cumulative dose (mg)	1,500	250 – 7,000	0 – 250 mg: 2 (2); 251 – 1,000 mg: 32 (25); 1,001 – 2,500 mg: 64 (50); 2,501 – 5,000 mg: 24 (19); 5,000 or + mg: 5 (4)
Time from diagnosis to first dose (days)	0	0 – 17	0 day: 69 (54); 1 day: 26 (21) ; 2 days: 1 (1); 3 – 5 days: 18 (14); 6 or + days: 13 (10)

TABLE 4 Adjusted mean or median (non-parametric test) difference in the time to event associated with different characteristics (multivariable linear regressions).

Subgroup	Covariables Included	Results (AZI – Untreated)	*p*
Sludge *N* controls = 6 *N* azithro = 48	Patient Group	14.346	0.438
	Gestational Age at Diagnosis	−0.725	**0.001**
	Bulging Membranes	−29.556	**0.023**
	Non-parametric tests	−21.5	0.441
Admission < 28 Weeks *N* controls = 104 *N* azithro = 106	Patient Group	−11.551	0.051
	Gestational Age at Diagnosis	−0.825	**<0.001**
	Preterm Labour	−15.093	**0.048**
	Bulging Membranes	−32.953	**<0.001**
	Type of Cerclage	16.072	**0.005**
	Progesterone treatment	10.140	0.114
Cerclage *N* controls = 29 *N* azithro = 44	Patient Group	−21.585	0.069
	Gestational Age at Diagnosis	−1.094	**<0.001**
	Bulging Membranes	−34.418	**0.014**
Emergency Cerclage *N* controls = 12 *N* azithro = 30	Patient Group	−4.021	0.834
	Gestational Age at Diagnosis	−0.916	**0.014**
	Bulging Membranes	−36.124	0.058
	Non-parametric tests	−32.5	0.172
Planned Cerclage *N* controls = 17 *N* azithro = 14	**Patient Group**	−43.914	**0.001**
	Gestational Age at Diagnosis	−1.037	**<0.001**
	Threatened Preterm Labour	−63.703	**0.001**
	Bulging Membranes	−76.990	**0.015**
	Progesterone treatment	29.545	0.073
	Antibiotics received *per hospital*	42.611	**0.004**
	Non-parametric tests	**−82**	**0.006**
Preterm Labour Started *N* controls = 38 *N* azithro = 26	Patient Group	0.802	0.863
	Bulging Membranes	−13.679	**0.005**
	Progesterone treatment	39.485	**<0.001**
	Non-parametric tests	4.5	0.355
Short Cervix *N* controls = 54 *N* azithro = 79	Patient Group	6.410	0.342
	Gestational Age at Diagnosis	−0.719	**<0.001**
	Bulging Membranes	−35.698	**<0.001**

doses were respectively 500 and 250 mg once a day for 4 days. Median cumulative dose was 1,500 mg and median delay from diagnosis to first dose was 0 day (Table 3). Ninety percent of treatments began within 5 days of diagnosis. When adjusted for confounders, there was no association between dose and time to composite event, (p=0.793).

In the subgroups analyses, there was no difference between groups in the following: sludge, emergency cerclage, preterm labour, short cervix (Table 4); however, each subgroup had a very limited number of women. A shorter pregnancy prolongation was found in the azithromycin group for the gestational age <28 weeks at diagnosis and the planned cerclage subgroup.

DISCUSSION

Several strategies have been used to prolong pregnancy in women a risk of preterm delivery. Antibiotics have been studied; however, studies using azithromycin in a North American population have never been published. In our study, the two time-to-event analyses did not show any effect of adding azithromycin to usual care to prolong pregnancy in women with intact membranes at risk of preterm delivery. In our institution, the usual care for the studied population includes tocolysis (high dose immediate release nifedipine with extended release maintenance and indomethacin), progesterone, cerclage if short cervix is present and penicillin G.

The effect of adding azithromycin to this treatment regimen was evaluated.

Strengths and limitations

The retrospective design allowed the evaluation of azithromycin in a real clinical setting, the inclusion of a large sample size favouring external validity and evaluation of several outcomes with a single exposure achieving multiple objectives. The use of a standardized data collection and time-to-event analyses also represent strengths, although the data collectors were not blinded. Inherent biases are included in our data. To reduce the influence of gestational age on the main outcome, we matched the patients (± 1 week, except for 16 patients at ±2 weeks and 6 patients at ±3 weeks) and other confounders were adjusted for in the statistical analyses. We could not adjust for all covariables, given their very low incidence. We were not able to match our patients for preterm birth risk factors given our small sample size. However, our subgroup analyses show a trend towards a negative treatment effect in selected subgroups of patients presenting important risk factors. Our sample size was not large enough to obtain a sufficient statistical power; 62% chance to detect a difference of 6.5 days to delivery. Finally, we did not exclude women with a diagnosis of chorioamnionitis. Diagnostic of chorioamnionitis is made when per partum fever is present and should not have had influenced the prescription of azithromycin on admission. Furthermore, since the only efficient treatment for chorioamnionitis is delivery, it was only considered as a confounding preterm birth risk factor. We could not include colonization with *mycoplasma* or *ureaplasma* in our analyses since we do not routinely screen patients for these bacteria.

Our results corroborate those of a 2002 Cochrane review of 11 randomized controlled trials (RCT) (7,428 women) which concludes antibiotics are not indicated to stop preterm labor in women with intact membranes.[15] No study evaluated azithromycin and 6,295 women came from a single study (ORACLE II).[24] This RCT (250 mg of erythromycin vs. 250 mg/125 mg amoxicillin/clavulanate vs. both vs. placebo) showed that no treatment prolonged pregnancy in any sub-analysis. These results are consistent with ours. Our study, however, also included patients whose preterm labour had not started yet. In our preterm labour subgroup, there was a non-statistically significant trend towards a pregnancy prolongation with azithromycin, (5.0 vs. 9.5 days; p=0.355) but it may be due to the use of progesterone, as shown in the linear regression (see Table 4).

In 2006, a RCT (erythromycin vs. placebo) including women with preterm labour and intact membranes, showed a significant prolongation of pregnancy with erythromycin (33.33 vs. 26.88 days, p <0.05).[23] In this study patients were tocolyzed before entering the RCT and those who had had a cerclage were excluded. It is, therefore, difficult to compare their results with ours since the population, the treatments used and the study design are different.

Some studies evaluated erythromycin in women at risk of preterm labour. A 2007 meta-analysis[25] of three RCTs concluded that erythromycin was associated with a lower risk of premature birth: HR=0.72; CI 95% 0.56−0.93. In our study, the rate of events at ≥37 weeks was not statistically different. However; the rate of events at ≥34 weeks was statistically different (HR=0.520; CI 95% 0.291−0.927) favouring the control group. These results may be attributable to the severity of the women's condition at admission in the azithromycin group. In addition, the only study in the meta-analysis that studied erythromycin alone included an intravaginal administration. The others evaluated combination of antibiotics.

Two RCTs were conducted in Malawi to evaluate azithromycin to prolong pregnancy. The APPLe study included 2,297 patients who received two 1-g doses of azithromycin, the first between 16 and 24 weeks and the second dose between 28 and 32 weeks versus placebo.[26] No significant difference was observed in the incidence of premature births (OR=0.96; CI 95% 0.76−1.21) or gestational age at birth. Preterm labor risk factors in Malawi, including hygiene conditions and malaria, are very different from those in a North American population. Furthermore, the results of APPLe were not stratified according to the presence/absence of other risk factors. Possible positive treatment effects could have been diluted. The second RCT evaluated azithromycin in association with sulfadoxin-pyrimethamine (SP) in 1,320 women

randomized into 3 groups: SP 2 doses versus SP 1 dose per month versus SP 1 dose per month with two 1-g doses of azithromycin.[27] The incidences of premature birth were respectively 17.9%, 15.4%, and 11.8% (p=0.01). The azithromycin group had a lower risk of low birth weight (p=0.02) and a higher gestational age at birth (p=0.03). The azithromycin group also had a lower risk of giving birth at <35 weeks (RR=0.48; CI 95% 0.26−0.89). As mentioned, it is difficult to extrapolate results from a Malawian population to ours.

A recent literature review by Mercer concluded that given the current paucity of evidence, antibiotic treatment in the setting of preterm labour with intact membranes should not be routinely offered.[28] We were not able to find any published study evaluating azithromycin, in a similar setting, even if it has become common practice in our hospital.

CONCLUSION

Azithromycin was added to medical therapy in a more at-risk population of pregnant women and no clear benefit was measured. These results challenge our current local practice. In order to evaluate the efficacy of azithromycin in this population, a prospective RCT comparing it to a placebo should be conducted. Neonatal consequences of exposure to azithromycin in terms of colonization, bacterial infections and bacterial resistance should be evaluated.

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Prior presentation

Our project has been presented as an abstract and short oral presentation form at the 67th Annual Clinical Meeting of the Society of Obstetricians and Gynecologists of Canada (June 21-25, 2011, Vancouver, BC, Canada) and at the Pharmacy Residents' Poster session on August 11, 2011, at the University of Montréal (Montréal, Qc, Canada).

Contribution to Authorship

I.G., G.F., N.R., C.M., MS.B, LM, EF contributed substantially to the conception, design, and interpretation of data. I.G., G.F., N.R., contributed substantially to acquisition of data. I.G., G.F., N.R., C.M., MS.B, EF contributed substantially to analysis of data.

I.G., G.F., N.R., drafted the article. I.G., G.F., N.R., C.M., MS.B, LM, EF revised it critically for important intellectual content.

I.G., G.F., N.R., C.M., MS.B, LM, EF approved the version to be published and accept responsibility for the paper.

Details of Ethics Approval

The study was approved by the Ethics and Research Committee and the Direction of Medical and University Affairs of Sainte-Justine UHC. No informed consent was required given the retrospective nature of the study.

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