Prolonged usage of intravaginal clindamycin cream combined with ampicillin for the management of PPROM - a case report

PPROM yönetiminde uzamış intravajinal klindamisin kremin ampisilinle birlikte kullanımı - bir olgu sunumu

Cihangir Mutlu Ercan[1], Ümit Aydoğan[2], Kazım Emre Karaşahin[1], İbrahim Alanbay[1], İskender Başer[1]

[1]Department of Gynecology and Obstetrics, Gülhane Military Medical Faculty, Ankara, Turkey

[2]Department of Family Medicine, Gülhane Military Medical Faculty, Ankara, Turkey

Abstract

Prolonged PPROM may be catastrophic both for the mother and fetus due to ascending infections. The decision was expectant management in the setting of a spontaneous preterm premature rupture of membranes (PPROM) case and the prevention of chorioamnionitis was essential. We aimed to describe maternal and neonatal outcomes in expectant management of PPROM beginning from the 24th gestational week (GW) of pregnancy up to the 34th week under treatment with continuous usage of intravaginal clindamycin cream. We concluded that expectant active management of PPROM with antibiotics may be a suitable treatment option in carefully selected patients after receiving the patient's approval. Intravaginal clindamycin cream may be combined with systemic antibiotics (ampicillin and erythromycin) and may be a maintenance single drug for the prophylaxis of ascending vaginal infections.

(J Turkish-German Gynecol Assoc 2011; 12: 124-6)

Key words: PPROM, Clindamycin vaginal cream, chorioamninitis

Received: 1 June, 2010 **Accepted:** 3 August, 2010

Özet

Uzamış PPROM asendan enfeksiyonlara bağlı anne ve bebek için oldukça kötü sonuçlar doğurabilmektedir. Spontan preterm ve prematür membran rüptürü (PPROM) ile müracaat eden olgumuzda, gelişebilecek koryoamnionit riskine karşı korunma zorunlu olup tedavi yaklaşımı ekspektan yönetim olarak belirlenmiştir. Amacımız 24. gebelik haftasında PPROM ile müracaat eden olgunun, 34. gebelik haftasına kadar intravajinal klindamisin kremin sürekli kullanımı ile takibi ve maternal, neonatal sonuçlarını tariflemektir. Sonuç olarak, PPROM olgularında antibiyotikler ile ekspektan aktif yönetim, dikkatli seçilmiş ve onamı alınmış olgularda uygun tedavi yaklaşımı olabilir. Asendan enfeksiyonlardan korunmada vajinal klindamisin sistemik antibiyotiklerle (ampisilin ve eritromisin) kombine tercih edilebileceği gibi idame tedavide tek ajan olarakta kullanılabilir.

(J Turkish-German Gynecol Assoc 2011; 12: 124-6)

Anahtar kelimeler: PPROM, Klindamisin vajinal krem, koryoamnionit

Geliş Tarihi: 01 Haziran 2010 **Kabul Tarihi:** 03 Ağustos 2010

Introduction

Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity. 25-30% of preterm deliveries follow preterm premature rupture of membranes (PPROM) which is defined as the spontaneous rupture of membranes before 37 completed weeks of gestation and before labor onset. It occurs in approximately 3% of pregnancies and is associated with significant

Maternal and neonatal infection, abruptio placenta, preterm delivery and cord prolapse are potential complications of PPROM. One-third of women with PPROM develop potentially serious infections, such as chorioamnionitis, endometritis or septicemia (1). The fetus and neonate are at maternal, fetal and neonatal risks. greater risk of PPROM-related morbidity and mortality than the mother, such as hyaline membrane disease, intraventricular hemorrhage, periventricular leukomalacia, infection (eg, sepsis, pneumonia, meningitis), and necrotizing enterocolitis. The rates of these morbidities vary with gestational age and are higher in the setting of chorioamnionitis (1).

Bacterial vaginosis is the overgrowth of vaginal mixed anaerobic flora over normal lactobacillary bacteria and is associated with serious perinatal complications such as miscarriage, preterm delivery and PPROM (2). The precise pathophysiology is peculiar, but ascending infection leading to endometrial inflammation is suspected. Here we would like to report a PPROM case in the setting of bacterial vaginosis in the previability zone which was managed successfully and yielded a healthy newborn.

Case Report

A 34-year old G2P1 patient was referred to Gulhane Military Medical Academy, Obstetrics and Gynecology department

Address for Correspondence: *Dr. Ümit Aydoğan, Department of Family Medicine, Gülhane Military Medical Faculty, Ankara, Turkey*
Phone: +90 312 304 31 43 e.mail: uaydogan06@gmail.com
doi:10.5152/jtgga.2011.28

due to rupture of the membranes at 24 weeks of pregnancy. Her first pregnancy was uneventful except for a cesarean section which was done due to a breech presentation. Until about 24 weeks, she was followed up in a primary health care unit. She had her last appointment 1 month previously for second trimester anomaly screening, which was reported as normal. Painless rupture of the membranes occurred 12 hours before her admission to our unit without any history of trauma. Obstetric ultrasonographic examination (Siemens Sonoline Antares™) revealed a live, 24 week-old, severe oligohydramniotic fetus with 30mm amniotic fluid index (AFI) and cervical length was verified by transvaginal probe as 35 mm. The fetal umbilical artery, ductus venosus and middle cerebral artery doppler indices were within normal limits. On sterile speculum examination, clear amniotic fluid passing from the external cervical os was seen by Valsalva maneuver and also thin homogenous vaginal discharge with a fishy odor was noticed. On wet mount of vaginal discharge, typical 'clue cells' were seen. No uterine contractions were identified by the tocometer probe. There was no sign of chorioamnionitis confirmed by her physical exam and laboratory findings. (Body temperature 36.8°C, blood pressure 110/70 mmHg, pulse rate 82/min, leukocyte count 8800/mm^3 with a sedimentation rate of 8mm/hr).

The therapy options and fetal-neonatal complications were discussed in detail with the family. Despite the fact that expectant management can lead to poor perinatal outcomes, the family decided to continue the pregnancy. After receiving a consent form from the family she was hospitalized. Due to PPROM, sulbactam sodium-ampicillin sodium IV 1 gr, q12hr was started and used for the first 48 hours and then erythromycin p.o. 500 mg, q8hr was used until the 10^{th} day. Clindamycin vaginal cream 2% q24hr was started concomitantly with Ampicillin therapy. Betamethasone in two divided doses of 12 mg was administered at twelve hour intervals. As there were no uterine contractions or sign of cervical dilatation, no tocolytic therapy was indicated.

One week later, in her examination; the discharge associated with bacterial vaginosis had disappeared but there was still some clear amniotic fluid oozing from the cervix. As the rupture of membranes was accompanied by active vaginosis, in order to minimize intrauterine infection risk, clindamycin therapy was continued once a day. After this initial treatment, she was followed-up bi-weekly by ultrasonography and her laboratory findings. Fetal growth indices were appropriate on her 28^{th} GW, and AFI was 52 mm. Since there was no sign of chorioamnionitis and the fetal status was reassuring, close follow-up was continued. AFI measurement at 30 and 32 weeks gestation were 54 and 58 mm respectively. Amniotic fluid oozing went on until the end of her pregnancy and so the clindamycin therapywas continued. Her pregnancy remained stable until 34 weeks of gestation when irregular contractions started and cervical dilation occurred. She underwent a repeat cesarean section; a 1840-gram healthy male fetus was delivered. The 5-minute Apgar score was 9. Postoperative course was uneventful both for the mother and newborn. The newborn did not develop respiratory distress syndrome and there was no sign of pulmonary hypoplasia, skeletal deformity or systemic infection as expected. He was followed up in the neonatal intensive care unit (NICU) for 1 week and finally discharged in a healthy condition with a follow-up appointment for developmental assessment.

Discussion

In the etiology and consequences of Premature Rupture of Membranes (PPROM), the gestational age and fetal status at membrane rupture have significant implications, thus maintaining and prolonging pregnancy has been the mainstay of the treatment. Starting at 23 weeks gestation, one week increments in gestational age are associated with substantial improvements in survival when delivery occurs between 23 and 32 weeks gestation (3). Nevertheless, in such conditions, if the clinician's decision is expectant, life-threatening risks such as stillbirth, maternal and perinatal infection-sepsis, abruptio placenta and oligohydramnios related conditions such as skeletal deformities, pulmonary hypoplasia and cord compression are probable complications and should always be kept in mind. These complications should always be discussed with the family before giving expectant management decision. In the present case we gained approximately 10 weeks by expectant management and this period is invaluable for a 24 week fetus.

Oligohydramnios was found to be associated with a shorter latency period in PPROM cases (4). Low amniotic fluid volume at admission has also been associated with adverse pregnancy outcomes. The pathophysiology still remains unclear. In the present case the patient was severely oligohydramniotic on admission but in her follow-up the amniotic fluid volume increased over time and it prevented the infant from worse complications such as pulmonary hypoplasia, facial deformation, and orthopedic abnormalities. So, the amniotic fluid volume is an important prognostic indicator for the assessment of neonatal outcome of the PPROM fetuses (5).

All women with PPROM should be monitored for signs of infection; these should include, routine clinical parameters; maternal temperature, uterine tenderness and contractions, maternal and fetal heart rate. Antibiotic therapy for PPROM is now routinely used and it is associated with prolonged time to delivery and reduced neonatal morbidity (6). The goal of antibiotic therapy is to reduce the frequency of maternal and fetal infection and delay the onset of preterm labor. The type and duration of antibiotic therapy vary in different studies (7) and there is no general consensus yet. Mine S. et al. concluded that continuous antibiotic prophylaxis in PPROM does not improve the outcome and its cost is ineffective. They suggest intermittent and short-term antibiotic prophylaxis as preferable to the continuous antibiotic prophylaxis in PPROM patients (8). In a recent Cochrane review, 14 placebo-controlled randomized trials involving over 6000 women evaluated the use of antibiotics following PPROM before 37 weeks of gestation (9). Compared to placebo/no treatment, antibiotic use was associated with a significant reduction in chorioamnionitis (RR 0.57, 95% CI 0.37-0.86), There was inadequate data to determine whether any antibiotic regimen (drug, dose, duration) was better than another, but macrolide antibiotics (eg, erythromycin) appeared to be safer than beta-lactam antibiotics (eg, amoxicillin-clavulanate),

as the latter were associated with an increased risk of necrotizing enterocolitis. In a review, ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours for 48 hours followed by amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours for 5 days was suggested (10).

We administered sulbactam-ampicillin IV 1 gr. bid as a starting regimen for the first 48 hours and then erythromycin p.o 500 mg bid was used until the 10th day. On the other hand clindamycin vaginal cream 2% once a day was started concomitantly with Ampicillin and used until delivery. This antibiotic regimen also provided adequate prophylaxis for Group B streptococcus (GBS), which is indicated in women whose GBS test results are positive or unknown.

An important infectious condition leading to PPROM and preterm birth is bacterial vaginosis. Bacterial vaginosis leads to a reduction in normal lactobacillar bacteria in vaginal flora and is caused by mixed anaerobic flora. Bacterial vaginosis is present in up to 20% of women during pregnancy (11) and the majority of these patients are asymptomatic. Endometrial inflammation and direct ascending bacterial invasion of the membranes are suspected, but the exact mechanism of how bacterial vaginosis leads to preterm birth is still unclear. The classical diagnosis of bacterial vaginosis is confirmed by the criteria of Amsel (12) and our case fulfills three out of four. The evidence to date does not suggest any benefit in screening and treating all pregnant women for asymptomatic bacterial vaginosis to prevent preterm birth (13). However, when bacterial vaginosis accompanies PPROM, in order to end this vicious circle, we usually prefer using antibiotics. The most widely used antibiotics for bacterial vaginosis are metronidazole and clindamycin, and we preferred clindamycin by vaginal route.

Clindamycin is categorized as Group B by FDA pregnancy risk categories. Fetal tissue levels increase following multiple dosing, with the drug concentrating in the fetal liver, but no reports linking the use of clindamycin with congenital defects have been reported (14). Usually one week of therapy is sufficient in pregnancy, but in association with PPROM, we used it as long as the passing of amniotic fluid continued for prophylaxis of ascending infections. This administration was not only for bacterial vaginosis but also to prevent other vaginal flora members which may reach the amniotic cavity. The possible emergence of resistance and fetal risks were our concern and further studies are needed to evaluate the benefit-hazard ratio. Although antibiotherapy seems to be beneficial in this case study, further investigations are needed to show their outcomes for prolonging latency durations of PPROM subjects. This possible limitation pertains to the generalizability of our study to the general population.

In conclusion, when PPROM is accompanied by bacterial vaginosis, expectant active management with corticosteroids and antibiotics may be suitable for carefully selected patients. In such a condition the final treatment option may be the patient's decision, which should be confirmed by a consent form. As we represent in our case, local clindamycin therapy may be a good choice for the prevention of ascending vaginal infections. Close and careful follow-up with appropriate antibiotics may prolong the latency period to bring a desperate fetus from the lower limits of viability to "life-zone".

Conflict of interest

No conflict of interest was declared by the authors.

References

1. Soraisham AS, Singhal N, McMillan DD, Sauve RS, Lee SK; Canadian Neonatal Network. A multicenter study on the clinical outcome of chorioamnionitis in preterm infants. Am J Obstet Gynecol 2009; 200: 372. [CrossRef]
2. Silver HM, Sperling RS, St Clair PJ, Gibbs RS. Evidence relating bacterial vaginosis to intraamniotic infection. Am J Obstet Gynecol 1989; 161: 808-12.
3. Goldenberg RL. The management of preterm labor. Obstet Gynecol 2002; 100: 1020-37. [CrossRef]
4. Park JS, Yoon BH, Romero R, Moon JB, Oh SY, Kim JC, et al. The relationship between oligohydramnios and the onset of preterm labor in preterm premature rupture of membranes. Am J Obstet Gynecol 2001; 184: 459-62. [CrossRef]
5. Huang S, Qi HB, Li L. Residue amniotic fluid volume after preterm premature rupture of membranes and maternal-fetal outcome. Zhonghua Fu Chan Ke Za Zhi 2009; 44: 726-30.
6. Aagaard-Tillery KM, Nuthalapaty FS, Ramsey PS, Ramin KD. Preterm premature rupture of membranes: perspectives surrounding controversies in management. Am J Perinatol 2005; 22: 287-97. [CrossRef]
7. Hutzal CE, Boyle EM, Kenyon SL, Nash JV, Winsor S, Taylor DJ, et al. Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a metaanalysis. Am J Obstet Gynecol 2008; 199: 1-8. [CrossRef]
8. Kermalli MS, Oğuz S, Danışman N, Gökmen O. Preterm Prematür Membran Rüptürlü Gebelerde Feto-Maternal Enfeksiyonun Erken Tahmininde Seri Nonstress Test (NST) Takibinin Rolü. Turkiye Klinikleri J Gynecol Obst 2000; 10: 91-7.
9. Kenyon, S, Boulvain, M, Neilson, J. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev 2003; CD001058.
10. Yudin MH, van Schalkwyk J, Van Eyk N, Boucher M, Castillo E, Cormier B, et al. Society of Obstetricians and Gynaecologists of Canada. Antibiotic therapy in preterm premature rupture of the membranes. J Obstet Gynaecol Can 2009; 31: 868-74.
11. Lamont RF. The role of infection in preterm labour and birth. Hosp Med 2003; 64: 644-7. [CrossRef]
12. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med 1983; 74: 14-22. [CrossRef]
13. McDonald HM, Brocklehurst P, Gordon A. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev 2007; 24: CD000262.
14. Philipson A, Sabath LD, Charles D. Transplacental passage of erythromycin and clindamycin. N Engl J Med 1973; 288: 1219-21. [CrossRef]