

Amoxicillin-clavulanic acid in women with preterm premature rupture of membranes and necrotizing enterocolitis in the newborns

© GinPolMedProject 4 (38) 2015

Review article

BARBARA ANNA KICEL-WESOŁOWSKA

Oddział Ginekologiczno-Położniczy SP ZOZ Wojewódzki Szpital Zespolony
im. J. Śniadeckiego w Białymstoku
Ordynator: prof. dr hab. Maciej Kinałski

Address for correspondence:

Barbara Anna Kicel-Wesołowska
Oddział Ginekologiczno-Położniczy SP ZOZ Wojewódzki Szpital Zespolony
im. J. Śniadeckiego
ul. Warszawska 15, 15-062 Białystok
tel. +48 692 173 367, fax +48 85 748 88 15, e-mail: barbara@kicel.pl

Statistic

Word count	1220
Tables	6
Figures	0
References	19

Received: 15.05.2015

Accepted: 24.07.2015

Published: 21.12.2015

Summary

Preterm premature rupture of membranes (PPROM) occurs before 37 completed weeks of pregnancy and is the cause of 30–40% of preterm births. This is due to the weakening of the structure of membranes, which is frequently induced by microbes. It carries a risk for newborns of not only many complications associated with prematurity, but also the development of sepsis, and that is why prophylactic antibiotic therapy in the case of preterm premature rupture of membranes is recommended. Therapeutic options include amoxicillin which is very often administered in combination with clavulanic acid. This medicine has been subjected to many tests in terms of the development of necrotizing enterocolitis in neonates born to mothers who have used it. However, the results of these research projects are not clear and do not allow these antibiotics to be linked to the development of such a complication in newborns.

Key words: amoxicillin-clavulanic acid, preterm premature rupture of membranes, necrotizing enterocolitis

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is observed before the 37th week of pregnancy and is a cause of approximately 1/3 of preterm labors in 2–4% of pregnancies [1,2]. It is caused by the weakening of the fetal membranes, which is usually induced by pathogens acting directly through proteases or phospholipases, or indirectly by activating collagenases that belong to the group of matrix metalloproteinases. The culture of the amniotic fluid of women with PPRM revealed pathogens in 32–35% of cases. The strongest relationship with chorioamnionitis has been observed for the following pathogens: *Gardnerella vaginalis*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*,

Neisseria gonorrhoeae, and other bacteria: B group streptococci, *Escherichia coli*, *Klebsiella spp.*, *Haemophilus influenzae* and *Mycoplasma hominis* [3].

Premature labor induced by fetal membrane rupture carries a risk of various complications associated with prematurity. Infection often results in sepsis. According to the guidelines of the American College of Obstetricians and Gynecologists (ACOG), if PPRM occurs, antibiotic therapy must be immediately initiated in order to reduce the risk of intra-amniotic infection. Subsequently, microbiological tests should be conducted, and, if needed, the treatment should be modified based on the findings. Taking into account the sensitivity of the pathogens mentioned above, it has

been determined that ampicillin and erythromycin should be administered intravenously for 48 h followed by amoxicillin and erythromycin orally for 5 days [4].

AMOXICILLIN

Amoxicillin is a beta-lactam antibiotic with antibacterial properties. It belongs to the aminopenicillin family and is characterized by the sensitivity to beta-lactamases (bacterial enzymes that break down beta-lactam bindings in an antibiotic molecule). It has a broad spectrum of activity, which is its great advantage. It exerts effects on both Gram (+) and Gram (-) bacteria (such as *Salmonella*, *Shigella*, *E. coli*, *Haemophilus influenzae*, *Bordetella pertussis* and *Proteus mirabilis*). The activity of amoxicillin towards G(+) pathogens is weaker than that of penicillin. However, it is 10 times stronger against G(-) bacteria. Its disadvantage is the susceptibility to the degradation by penicillinases (enzymes belonging to beta-lactamases). It is therefore not very effective in infections induced by bacteria that produce this enzyme. However, the combination of this antibiotic with clavulanic acid (a beta-lactamase inhibitor) enabled its spectrum of activity to be broadened to include numerous bacteria that produce such enzymes [5]. Amoxicillin with clavulanic acid, i.e. popular Augmentin, Amoxi-clav, etc., is frequently used in various infections in pregnant women, also in the case of PPRM.

PRETERM PREMATURE RUPTURE OF FETAL MEMBRANES

Preterm premature rupture of fetal membranes complicates 2–4% of single and 7–20% of multiple pregnancies. It is the main cause of preterm labors and contributes to 18–20% of perinatal mortality of neonates in the United States of America [6]. Of note is the fact that

women who developed PPRM once are more often observed to have the same complication in their subsequent pregnancies. Recent studies indicate that the risk of preterm premature rupture of fetal membranes is correlated with the level of human beta-defensin 2 (HBD2). Defensins, produced by epithelial cells, are characterized by antibacterial, antifungal and antiviral properties. HBD2 levels are stable in the second and third trimesters of normal pregnancy and increase in the case of infections [7]. Apart from the aforementioned chorioamnionitis, other PPRM risk factors include: premature placental detachment, peripartum vaginal bleeding, uterine defects (including a uterine septum), uterine overdistention (polyhydramnios, multiple pregnancy), cervical insufficiency, uterine invasive procedures (amniocentesis, chorionic villus sampling, fetoscopy), etc. [8].

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) in newborns is characterized by the presence of septic necrosis of the intestinal wall, which can affect the wall on its entire thickness and lead to its rupture. These changes can occur both in the small and large intestine and can be multifocal. The etiology of NEC has not been fully elucidated. There are many risk factors of this disease, both newborn- and mother-related. Necrotizing enterocolitis is mostly correlated with extremely low birth weight and gestational age below 28 weeks [9]. Randomized studies conducted by British authors (ORACLE I and II) concerned the use of antibiotics in women with PPRM. The study assessed the effects of erythromycin and the use of amoxicillin with clavulanic acid [10]. It revealed a relationship in using the combination of amoxicillin with clavulanic acid (as a monotherapy or in combination with erythromycin) with the

Tab. 1. Influence of amoxicillin with clavulanic acid and erythromycin on NEC in newborns. (ORACLE I)

NEC	only AC	AC and AC+E	no AC	only P	E+AC	only E	E and E+AC	no E
suspected or verified	50 (4,1%)	92 (3,8%)	58 (2,4%)	33 (2,7%)	42 (3,5%)	25 (2,1%)	67 (2,8%)	83 (3,4%)
verified	24 (1,9%)	44 (1,8%)	17 (0,7%)	6 (0,5%)	20 (1,7%)	11 (0,9%)	31 (1,3%)	30 (1,2%)

AC – amoxicillin with clavulanic acid; E – erythromycin; P – placebo

Tab. 2. Influence of amoxicillin with clavulanic acid and erythromycin on NEC in newborns (ORACLE II)

NEC	only AC	AC and AC+E	no AC	only P	E+AC	only E	E and E+AC	no E
suspected or verified	19 (1,2%)	42 (1,4%)	28 (0,9%)	12 (0,8%)	23 (1,5%)	16 (1,0%)	39 (1,2%)	31 (1,0%)
verified	9 (0,6%)	20 (0,6%)	10 (0,6%)	4 (0,3%)	11 (0,7%)	6 (0,4%)	17 (0,5%)	13 (0,4%)

development of necrotizing enterocolitis in newborns (from 1 July 1994 to 31 May 2000). The ORACLE I demonstrated absolute risk increase of NEC by approximately 1.5% compared with newborns who have not been prenatally exposed to this antibiotic (Tab. 1). Authors of other studies suggest that this phenomenon can result from antibiotic use and be associated with disorders in the process of gastrointestinal colonization in newborns [11].

The ORACLE II (Tab. 2) also indicates the increased incidence rate of NEC in newborns prenatally exposed to amoxicillin with clavulanic acid, although it is not as evident as in the first study.

In other retrospective studies conducted by American researchers based on the incidence on NEC in 1988–2006 in Mount Sinai School of Medicine [12], the action of ampicillin in monotherapy, combined therapy and in combination with sulbactam was compared. The studies revealed increased incidence of NEC in newborns whose mothers used ampicillin (97 newborns), in both monotherapy and combined treatment (Tab. 3).

Other randomized trials conducted by American physicians as part of the Maternal-Fetal Medicine Units Network do not confirm the correlation of amoxicillin and ampicillin with necrotizing enterocolitis in newborns. On the contrary, they demonstrate decreased incidence of this complication (Tab. 4) [13]. Moreover, following an analysis of preterm newborns prenatally exposed to amoxicillin with clavulanic acid in 1983–

2000 in Liverpool, Al-Sabbagh, Moss and Subhedar did not find a proof for NEC development (Tab. 5) [14]. Similarly, the authors of a retrospective analysis conducted in 1999–2006 in California also reject the hypothesis that the risk of NEC is increased by amoxicillin with clavulanic acid or ampicillin with sulbactam (Tab. 6) [15].

In a retrospective study conducted in the Polish Clinic of Perinatology at the Polish Mother's Memorial Hospital, the authors did not observe any relationship between using beta-lactams and increased incidence of necrotizing enterocolitis in newborns [16].

CONCLUSION

The studies conducted so far result in different, sometimes conflicting conclusions concerning the influence of amoxicillin with clavulanic acid on NEC in neonates whose mothers' pregnancies were complicated with PPRM. Some authors confirm this thesis, and some refute it. All studies, however, unanimously prove that maternal administration of antibiotics helps reduce prematurity with all its complications. The studies support the opinion that antibiotic therapy reduces the number of chorioamnionitis events in the placenta and the incidence of sepsis in newborns [17,18]. Despite their benefits, there is no consensus as to the influence of antibiotics on NEC in newborns. It seems reasonable to evaluate the need for using amoxicillin with beta-lactamase inhibitors in preterm premature rupture of fetal membranes and to consider replacing them with

Tab. 3. Influence of various antibiotics used by the mother before delivery on NEC

Antibiotic	Newborns with NEC	Control group
Ampicillin	26	11
Ampicillin in monotherapy and combined treatment	28	10
Ampicillin + sulbactam	5	1
Erythromycin	8	8
Gentamicin	4	2
Cefazolin	6	8
Clindamycin	1	4
Piperacillin	7	7

Tab. 4. Relationship of prenatal exposure to antibiotics with NEC in newborns [13]

	Antibiotic therapy*	Placebo
Incidence of NEC	2,3%	5,8%

*Ampicillin + Erythromycin i.v. for 48 h followed by amoxicillin and erythromycin p.o.

Tab. 5. Prenatal exposure to amoxicillin with clavulanic acid [14]

	Newborns with NEC	Control group
Prenatal exposure to amoxicillin with clavulanic acid	5	11

Tab. 6. Comparison of various antibiotic groups in terms of increased risk of NEC in newborns [15]

Antibiotics used	Ampicillin + sulbactam i.v. followed by amoxicillin with clavulanic acid p.o.	Cefazolin + Erythromycin i.v. followed by Cefalexin + Erythromycin p.o.
NEC in newborns	8,0%	10,2%

antibiotics of a different group, e.g. macrolide erythromycin. The experts of the Polish Gynecological Society and Polish Society of Perinatal Medicine propose that intra-amniotic infection in the course of preterm outflow of amniotic fluid should be treated with ampicillin and gentamycin. In patients with hypersensitiv-

ity to penicillins, ampicillin can be replaced with erythromycin or first-generation cephalosporin [19]. Using amoxicillin with clavulanic acid is not a mistake. An obstetrician is left with a choice: either continue the “traditional” antibiotic therapy or administer drugs of other groups.

References:

1. **Romero R, Athayde N, Maymon E et al.** Premature rupture of membranes. *Medicine of the fetus and mother*. Philadelphia: Lippincott-Raven, 1999: 1581-1625.
2. **Deering SH, Patel N, Spong CY, Pezzullo et al.** Fetal growth after preterm premature rupture of membranes: is it related to amniotic fluid volume? *The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. 2007;5 (20):397-400.
3. **Gomez R, Romero R, Mazor M et al.** The role of infection in preterm labour. Edinburgh: Churchill and Livingstone. 1997;85-126.
4. **Clinical Management Guidelines for Obstetrician-Gynecologists** Nr 139, Premature rupture of membranes. *Obstetrics & Gynecology* 2013;122:918-930.
5. **Kostowski W, Herman ZS.** Farmakologia – podstawy farmakoterapii: podręcznik dla studentów medycyny i lekarzy. Wyd. 3 poprawione i uzupełnione. Warszawa. PZWL.2006; 1569.
6. **Caughey AB, Robinson JN, Norwitz ER.** Contemporary Diagnosis and Management of Preterm Premature Rupture of Membranes. *Review in Obstetrics & Gynecology* 2008;vol. 1, No. 1:11-22.
7. **Couteau C, Haumonte JB, Bretelle FW et al.** Management of preterm and prelabour rupture of membranes in France. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction* 2013;42 (1):21-28.
8. **ACOG Committee on Practise Bulletins-Obstetrics.** ACOG Practise Bulletin No. 80: premature rupture of membranes . Clinical management guidelines for obstetrician-gynecologists. *Obstetrics and Gynecology* 2007;109:1007-1019.
9. **Krakós M, Krajewski P, Bernas S. i wsp.** Martwicz zapalenie jelit (NEC) u noworodków ze skrajnie niską wagą urodzeniową (ELBW) — doświadczenie jednego ośrodka (praca oryginalna). *Chirurgia Polska Via Medica* 2007;9;2:78-84.
10. **Kenyon SL, Taylor DJ, Tarnow-Morodi W.** - for the ORACLE Collaborative Group Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE randomised trial. *Lancet* 2001;357:979-988. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001;357:989-994.
11. **Langerhendries JP, Denoel A, Rousseaux D.** Antibiotics in pregnancy: importance of rational utilization. *Rev Med Liege* 2000;55:775-781.
12. **Weintraub AS, Ferrara L, Deluca I et al.** Antenatal antibiotics exposure in preterm infants with necrotising enterocolitis. *Journal of Perinatology* 2012;32:705-709.
13. **Mercer BM, Miodovnik M, Thurnau GR et al.** Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. *JAMA* 1997;278(12):989-995
14. **Al-Sabbagh A, Moss S, Subhedar N.** Neonatal necrotising and perinatal exposure to co-amoxycylav. *Archives of Disease in Childhood. Fetal and Neonatal Edition*. 2004;89:F187.
15. **Ehsanipoor R, Chung J, Clock C et al.** A retrospective review of ampicillin-sulbactam and amoxicillin+clavulanate versus cefazolin/cephalexin and erythromycin in the setting of preterm premature putpure membranes: maternal and neonatal outcomes. *American Journal of Obstetrics and Gynecology* - supplement to December 2007.
16. **Pięta-Dolińska A, Woźniak P, Jaczewski B i wsp.** Leczenie antybiotykami porodów przedwczesnych – praca przesłana na Sympozjum V Poznańskie Dni Medycyny Perinatalnej, listopad 2001.
17. **Gibbs RS, Eschenbach DA.** Use of antibiotics to prevent preterm birth. *American Journal of Obstetrics and Gynecology* 1997;177:375-380.
18. **Egarter C, Leitich H, Husslein P et al.** Adjuvant antibiotic treatment in preterm labour and neonatal morbidity: a meta-analysis. *Obstetrics and Gynecology* 1996;88:303-309.
19. **Bręborowicz GH, Paszkowski T, Dębski R.** Rekomendacje dotyczące profilaktyki, diagnostyki i postępowania w zagrażającym porodzie przedwczesnym. Zespół ekspertów PTG i PTMP. Poród przedwczesny. OWN. Poznań 2006;241-51.