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Coll. Antropol. **38** (2014) 2: 653–657
Original scientific paper

The Role of Antibiotic Prophylaxis in Preterm Premature Rupture of Membranes

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A B S T R A C T

Preterm premature rupture of membranes (PPROM) occurs in 3 percent of all pregnancies and is responsible for, or associated with, approximately one-third of preterm births causing significant perinatal morbidity and fetal death. Preterm infants are very vulnerable to respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), other neurological sequelae, infection and necrotizing enterocolitis (NEC). Chorioamnionitis based on clinical criteria occurs in approximately 3–30% of all PPROM pregnancies. The aim of this study was to analyze the role of antibiotic prophylaxis in delivery delay on neonatal outcome (body weight, Apgar scores, pulmonary complications, neurological complications – abnormal cerebral ultrasound scan prior to hospital discharge, perinatal infections) and to determine the possibility of an optimal antibiotic regimen. Therefore we retrospectively analyzed last 5 years of data from patients treated in our center and provided a coherent overview of the clinical course and outcome of patients with PPROM treated with prophylactic antibiotics and antenatal corticosteroids. There were 324 preterm newborns which fulfilled the inclusion criteria for our study; 190 in Study group (received empiric i.v. antibiotics) and 134 in Control group (without antibiotic). We found significant difference in gestational age ($p<0.0001$), birth weight ($p<0.0001$), Apgar scores ($p<0.0001$) maternal C-reactive protein level ($p<0.0001$) and latency period (5.54 days vs. 11.33 days, $p=0.001$) between the groups. Histologic chorioamnionitis was significantly more frequent in s Study group (14.2% vs. 36.3%, $p<0.0001$). We found significant difference in neonatal outcome according the different antibiotic treatment. Antenatal antibiotics and corticosteroid therapies have clear benefits and should be offered to all women without contraindications.

***Key words**: PPROM, antenatal antibiotics, neonatal outcome, chorioamnionitis*

Introduction

Premature rupture of membranes (PROM) is defined as a rupture of amniotic membranes before the onset of uterine contractions. Preterm PROM (PPROM) is the term used when the pregnancy is less than 37 completed weeks of gestation. PPROM occurs in 3 percent of all pregnancies and is responsible for, or associated with, approximately one-third of preterm births causing significant perinatal morbidity and fetal death. The management of PPROM is among the most controversial issues in perinatal medicine, especially regarding duration of administration and type of antibiotic prophylaxis. The fetus and neonate are at greater risk of PPROM related morbidity and mortality then the mother. Majority of pregnancies complicated with PPROM deliver preterm and within one week of membrane rupture. The pathogenesis of PPROM is not completely understood. Preterm infants are very vulnerable to respiratory distress syndrome, intraventricular hemorrhage, periventricular leucomalacia, other neurological sequelae, infection, and necrotizing enterocolitis. The rates of these morbidities are higher in the setting of chorioanionitis[1]. The risk of placental abruption is seven to nine fold increased in pregnancies with PPROM if infection is present[2]. The risk of PPROM have generally been viewed as those of infection in opposition to those of prematurity. Neonatal sepsis is documented in less than 10%, and chorioamnionitis based on clinical criteria occurs in approximately 3–30% of all PPROM pregnancies[2]. Subclinical infections based on positive amniotic fluid culture or histologic inflammation of the umbilical cord or membranes is seen

Received for publication February 17, 2014

up to 80%[2]. The reoccurrence rate for PPROM is up to 30%. Progesterone therapy and bacterial vaginosis treatment appears to be effective in reducing the risk of reoccurrence preterm birth caused by PPROM[3]. The goal of antibiotic therapy is to reduce the frequency of maternal and fetal infection and to delay the onset of preterm labor. As the oldest and largest third level maternity center in Croatia, Department for Obstetrics and Gynecology, University Hospital Centre Zagreb in year 2012 had 4159 deliveries, 359 newborns (7.9%) were preterms. Perinatal mortality rate was 3.6‰. Therefore we retrospectively analyze last 5 years of data from patients treated in our center and provided a coherent overview of the clinical course and outcome of patients with PPROM treated with prophylactic antibiotics and antenatal corticosteroids. Here we present conclusions regarding the latency period, maternal and neonatal morbidity and mortality in patients with PPROM. The aim of this study was to analyze the role of antibiotic prophylaxis in delivery delay on neonatal outcome (body weight, Apgar scores, pulmonary complications, neurological complications – abnormal cerebral ultrasound scan prior to hospital discharge, perinatal infections) and to determine the possibility of an optimal antibiotic regimen.

Materials and Methods

As a third level perinatal center, the neonatal intensive care unit (NICU) of Department for Obstetrics and Gynecology, University Hospital Centre Zagreb takes care of over half preterm newborns in Croatia. The study retrospectively analyzed all newborns born prior to 37 weeks of gestation from singleton pregnancies complicated with PPROM from January 2008 until December 2012. Preterm newborns with fetal and chromosomal anomalies and preterm newborns from pregnancies complicated with preeclampsia, HELLP syndrome, gestational diabetes mellitus and chronic diseases were excluded from the study. PPROM was confirmed by clinical examination and with Amnisure® test. Chorioamnionitis was diagnosed if two or more findings were present: maternal fever <38°C, maternal tachycardia (>100/min), uterine fundal tenderness, vaginal discharge and purulent or foul amniotic fluid, fetal tachycardia (>160/min), maternal leukocytosis >12x10/L and elevated levels of C-reactive protein. Gestational age at delivery was determined as period from last menstrual period or from fetal ultrasound findings. Tocolysis was started in both groups until 34 weeks of gestation during which time corticosteroids were administered. Patients from Study group received empiric i.v. antibiotics. Control group was without antibiotic prophylaxis. Neonatal outcome parameters included gestational age at birth, birth weight, Apgar score, perinatal infection, abnormal brain ultrasound findings, respiratory distress syndrome (RDS) and neonatal death. Diagnosis of perinatal infection was based on clinical examination of the infant and laboratory findings at 12 to 36 hours after birth such as white count, absolute neutrophil count, immature neutrophil count, absolute band count and C-reactive protein level. Diagnosis of respiratory distress syndrome (RDS) was based on clinical findings, low oxygen saturation, respiratory acidosis and chest X-ray. Abnormal brain ultrasound findings included intraventricular haemorrhage (IVH) and

TABLE 1
MATERNAL AND NEONATAL CHARACTERISTICS

	Control group (N=134)	Study group (N=190)	p value
Gestational age (weeks)	33.17±2.6	31.26±3.9	<0.0001
Birth weight (grams)	2048±597	1703±592	<0.0001
White blood cells mothers (10^9/L)	12.8±3.7	13.91±3.9	0.029
C-reactive protein (g/L)	11.87±21	21.74±25	<0.0001
Latency period (days)	5.54±10.75	11.33±14.09	0.001
Positive umbilical cord blood culture (%)	81.5	88.6	0.046
Perinatal infections (%)	56.7	65.8	0.153 NS
Sepsis (%)	4.5	10	0.050
Abnormal brain US (%)	6.7 IVH; 0 PVL	4.2 IVH; 3.1 PVL	0.067 NS
RDS (%)	20.1	27.4	0.086 NS
Antenatal corticosteroids (%)	64.9	92.1	0.029
Transport in utero (%)	36.6	53.7	0.002
Histologic chorioamnionitis (%)	14.2	36.3	<0.0001
Apgar 1st min (1–10)	6.79	7.95	<0.0001
Apgar 5th min (1–10)	8.00	8.84	<0.0001
Cervical smear Ureaplasma/Mycoplasma/ Chlamydia (%)	8	18	0.040
Neonatal death (%)	4.5	8.4	0.165

IVH– intraventricular haemorrhage; PVL – periventricular leukomalacia; RDS – respiratory distress syndrome

white matter damage. Intraventricular haemorrhage was diagnosed following Volpe's criteria and graded from I to IV (gr I–IV). White matter damage included periventricular leukomalacia (PVL). All preterm newborns are treated in NICU. For statistical comparison of results between groups we used chi-square test and Mann-Whitney test.

Results

There were 324 preterm newborns which fulfilled the inclusion criteria for our study; 190 in Study group and 134 in Control group. Control group included newborns prior to 37 weeks of gestation from singleton pregnancies complicated with PPROM but without antibiotic prophylaxis during the latency period. Preterm newborns with fetal and chromosomal anomalies and preterm newborns from pregnancies complicated with preeclampsia, HELLP syndrome, gestational diabetes mellitus and chronic diseases were excluded from the control group. Maternal and neonatal characteristics for all premature newborns are shown in Table 1. We found significant difference in gestational age (33.17 weeks *vs.* 31.26 weeks, $p<0.0001$), birth weight (2048 g *vs.* 1703 g, $p<0.0001$), Apgar scores in 1st (6.79 *vs.* 7.95, $p<0.0001$) and 5th (8.00 *vs.* 8.84, $p<0.0001$)) minute, maternal white blood cells count ($12.8x10^9$ *vs.* $13.91x10^9$, $p=0.029$) and C-reactive protein level (11.87 *vs.* 21.74, $p<0.0001$), latency period (5.54 days *vs.* 11.33 days, $p=0.001$) and antenatal corticosteroid administration (64.9% *vs.* 92.1%, $p=0.029$) between the groups. Histologic chorioamnionitis was significantly more frequent in Study group (14.2% *vs.* 36.3%, $p<0.0001$), too. 10.8% preterm newbornshad extremely low birth weight, and 57 newborns (19.7%) low birth rate, with significant difference between the groups; $p<0.0001$ (Figure 1) More extremely low gestational age newborns were in Study group, too (Figure 1). We found significantly longer latency period in Study group; $p=0.001$ (Figure 2). More pregnancies from control group finished within first 72 hours; $p<0.01$ (Table 2).

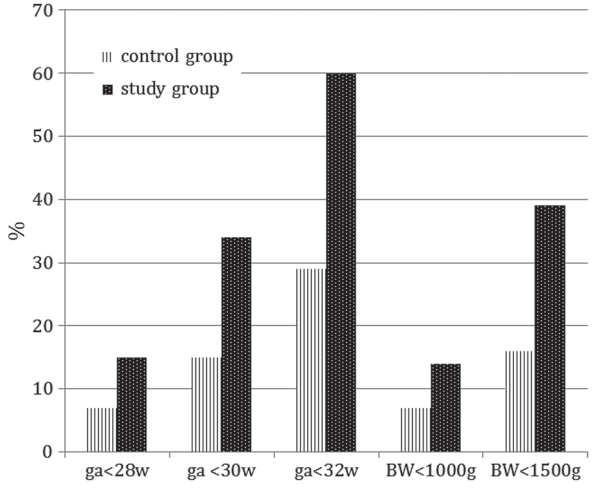

Fig. 1. Birth weight and gestational age between the groups. Ga – gestational age (weeks), bw – birth weight (grams), p<0.0001.

TABLE 2
PREGNANCIES FINISHED WITHIN 72 HOURS

	Study group (N=190)	Control group (N=134)
<24 hours (%)	3.2	10.4
24–48 hours (%)	8.9	25.4
48–72 hours (%)	10.0	22.4
Total (%)	22.1	58.2

$p<0.001$

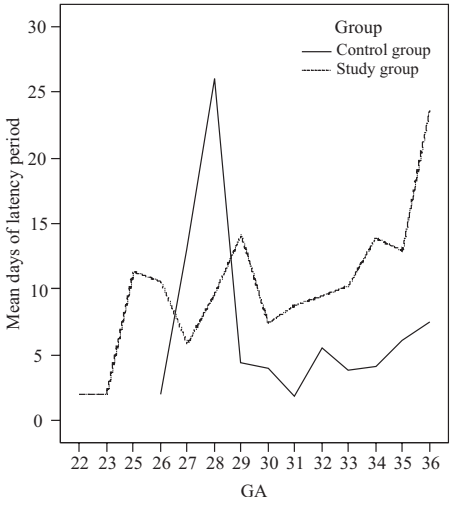

Fig. 2. Latency period. Ga – gestational age (weeks), p=0.001.

Type of antibiotic treatment had significant impact on prolongation of pregnancy after PPROM (Figure 3). We found significant difference in neonatal outcome according the treatment option (Table 3). Antibiotic prophylaxis regimen in pregnancies complicated with PPROM varies considerably regarding the regional hospitals that patients were transferred from.

Discussion

Preterm delivery accounts for 80% of perinatal mortality and more than half of the long-term morbidity. Effective treatment relies on accurate diagnosis and depends on gestational age. PPROM is associated with significant maternal and neonatal morbidity and mortality from infection, umbilical cord compression, placental abruption and preterm birth. Subclinical intrauterine infection has been implicated as a major etiological factor in the pathogenesis and subsequent maternal and neonatal morbidity associated with PPROM. In the past, management of women with PPROM was expectant, without any medications. Several studies reported that the latency period after PPROM was 1.5–4.6 days[4–6], which is comparable with our control group, but different from our study group where latency period was prolonged (Table 1). Fifty to ninety-three percent of cases and 69.3–97.3% cases delivered within 48 hours and 7 days follow-

TABLE 3
ANTIBIOTIC REGIMEN AND NEONATAL OUTCOME

	Amino-glycosides N=43	Cephalosporins N=72	Betalactams N=18	Combination N=57	p value
Positive umbilicalcord blood culture (%)	8.8	14	13	10	0.046
Histologic – Chorioamnionitis (%)	34	33	44.5	38.6	<0.0001
Perinatal infections (%)	60	66.7	66.7	68	NS
Sepsis (%)	14	8.3	5.6	11.1	NS
Abnormal brain ultrasound (%)	7	7	0	10.5	NS 0.068

ing rupture of membranes, respectively[7,8]. We found 58% of our control group patients delivered within first 72 hours (Table 2). After two large, randomized controlled trials, prolongation of latency period is believed to reduce neonatal complications[9,10]. Thus, the American College of Obstetricians and Gynecologists prepares guidelines using prophylactic antibiotics in the expectant management of PPROM to prolong pregnancy, reduce maternal infectious morbidity and reduce infectious and gestational age-dependent neonatal morbidity. Corticosteroids are recommended to administer in PPROM to reduce the risk of neonatal prematurity related complications[11]. In high-income countries, it is standard practice to give antibiotics to women with preterm PPROM to delay birth and reduce the risk of infection. In low and middle-income settings, where some 2 million neonatal deaths occur annually due to complications of preterm birth or infection, many women do not receive antibiotic therapy for PPROM[3]. Chorioamnionitis is associated with 20–40% of cases of early neonatal sepsis and pneumonia. Recent data has suggested that exuberant fetal immune response to intraamniotic infection is associated with white matter brain injury and cerebral palsy[12]. We found significant difference in reduction of chorioamnionitis between the groups (14.25% *vs*. 36.3%), but no difference in fetal brain ultrasound scan (6.7% *vs*. 4.2%). We observed higher chorioamnionitis rate in the study group, possibly due to longer latency period. Chorioamnionitis is polymicrobial, primarily due to ascending colonization or infection. Two-thirds of women with chorioamnionitis have at least two isolates per specimen of amniotic fluid. Regardless of gestational age, genital mycoplasmas are the most common isolates. Genital mycoplasmas are highly prevalent (>70%) in the lower genital tract and their pathogenicity is controversial. We found them present in 18% of patients in our control group (Table 1). For this reason, some authors attribute their isolation from patients with chorioamnionitis to contamination or colonization from the lower tract, rather than a true infection. However, there is increasing support of their pathogenicity, including induction of a robust inflammatory response with clinical consequences for both mother and neonate[13]. Measurement of maternal inflammatory response (C-reactive protein >2 mg/dL) is not useful for prediction of early intraamniotic infection[14], but we found it significantly different (11.8 *vs*. 21.74; p<0.0001). Novel proteomic biomarkers in the amniotic fluid or in the maternal serum are under investigation in an attempt to identify unique proteins diagnostic of subclinical chorioamnionitis[14]. Preliminary studies show promise in the diagnosis of early intraamniotic infection[15]. A regimen with reasonable activity against the major pelvic pathogens should be used[16]. In our hospital there is no written protocol for antibiotic prophylaxis in case of PPROM, but a recommendation in administering a seven-day course of antibiotic prophylaxis to all women with PPROM who are being managed expectantly. Chemoprophylaxis we used in last 5 years is showed in Figure 3. We found significant difference in gestational age and birth weight (Figure 2; p<0.0001) and latency period (Figure 3; p= 0.001) in study group. The preference is to give ampicillin 2 g intravenously every six hours for 48 hours, followed by amoxicillin (500 mg orally three times daily or 875 mg orally twice daily) for an additional five days with one dose of azithromycin(one gram orally) upon admission. Ampicillin specifically targets group B streptococcus, many aerobic gram-negative bacilli, and some anaerobes. Azithromycin specifically targets genital mycoplasmas, which can be important causes of chorioamnionitis in this setting, and also provides coverage of Chlamydia trachomatis[17] which is an important cause of neonatal conjunctivitis and pneumonitis. We found different treatment options regarding the duration of PPROM (Figure 3) with significant difference in appearance in histologic chorioamnionitis (Table 3; p<0.0001). Despite lack of unified strategy, our study clearly documented that antibiotic prophylaxis leads to prolonged latency period in

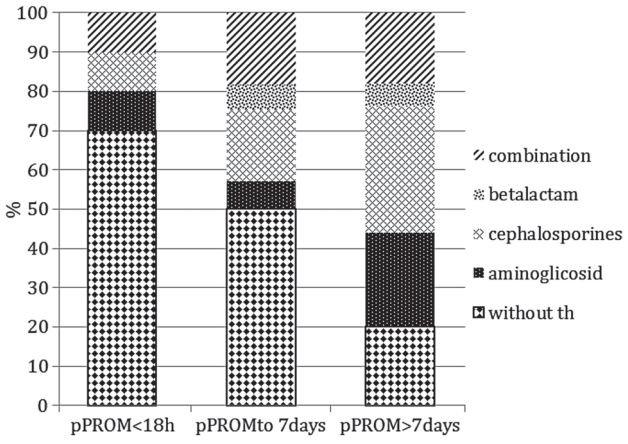

Fig. 3. Treatment option and duration of pprom, p<0.001.

PPROM. This is followed with prolongation of pregnancy, advanced fetal maturity and higher Apgar scores in first and fifth minutes. Choice of prophylactic antibiotic regimen is at the moment in our country inconsistent. This data support the need for unified antibiotic prophylactic strategy. Recent Cochrane study which included 22 trials, involving 6832 women and newborns certify that routine prescription of antibiotics for women with preterm rupture of membranes is associated with prolongation of pregnancy and improvements in a number of short-term neonatal morbidities, but no significant reduction in perinatal mortality[18]. Our study found similar results (Table 1).

Conclusion

Antenatal antibiotics and corticosteroid therapies have clear benefits and should be offered to all women without contraindications. The antibiotic of choice is not clear but co-amoxiclav should be avoided in women due to increased risk of neonatal necrotizing enterocolitis[18]. During conservative management, women should be monitored closely for placental abruption, infection, labor and a non-reassuring fetal status. Women with PPROM after 32 weeks of gestation should be considered for delivery, and after 34 weeks the benefits of delivery clearly outweigh the risks[19].

REFERENCES

1. SORAISHAM AS, SINGHAL N, MCMILLAN DD, SAUVE RS, LEE SK, American Journal of Obstetrics and Gynecology 200 (2009) 372. — 2. ANANTH CV, OYELESE Y, SRINIVAS N, YEO L, VINTZILEOS AM, Obstet Gynecol, 1104 (2004) 71. — 3. CONSENS S,BLENCOWE H, GAVETT M, LAWN JE, Int J Epidemiol, 39 (2010) 134. — 4. PHUPONG V, TANEEPANICHSKUL S, J Paediatr Obstet Gynecol, 29 (2003) 25. — 5. NELSON LH, ANDERSON RL, O' SHEA TM, Am J Obstet Gynecol. 171 (1994) 350. — 6. MERCER BM, CROCKER LG, BOE NM, SIBAI BM, Am J Obstet Gynecol, 169 (1993) 775. — 7. GRAHAM RL, GILSTRAP LC 3RD, HAUTH JC, KODACK-GARZA S, CONASTER DG, Obstet Gynecol, 59 (1982) 607. — 8. COX SM, WILLIAMS ML, LEVENO KJ, Obstet Gynecol, 71 (1988) 558. — 9. KENYON SI, TAYLOR DJ, TARNOW-MORDI W, Lancet, 357 (2001) 979. — 10. MERCER BM, MIODOVNIK M, THURNAU GR, GOLDENBERG RL, DAS AF, RAMSEY RD, RABELLO YA, MEIS PJ, MOAWAD AH, IAMS JD, VAN DORSTEN JP, PAUL RH, BOTTOMS SF, MERENSTEIN G, THOM EA, ROBERTS JM, MCNELLIS D, JAMA, 278 (1997) 989. — 11. ACOG PRACTICE BULLETIN, Obstet Gynecol, 109 (2007) 1007. — 12. CORNETTE L, Semin Fetal Neonatal Med, 9 (2004) 459. — 13. WAITES KB, KATZ B, SCHELONKA RL, Clin Microbiol Rev, 18 (2005) 757. — 14. BUHIMSCHI IA, ZAMBRANO E, PETTKER CM, BAHTIYAR MO, PAIDAS M, ROSENBERG VA, THUNG S, SALAFIA CM, BUHIMSCHI CS, Obstet Ginecol, 111 (2008) 403. — 15. HITTI J,LAPIDUS LA, XINFANG L, REDDY AP,JACOB T, DASARI S, DAVID A. ESCHENBACH DA,GRAVETT MG, NAGALLA SR, Am J Obstet Gynecol, 203 (2010) 32. — 16. ACOG COMITEE OPINION NO.445, Obstet Gynecol, 114 (2009) 1159. — 17. WORKOWSKI KA, BERMAN S, CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), MMWR Recomm Rep, 59 (2010) 1. — 18. KENYO S, BOULVAIN M, NEILSON JP, Cochrane Database Syst Rev, 2013. — 19. PASSOS F, CARDOSO K, COELHO AM, GRACA, A, CLODE N, MENDES DA GARCA L, Obstet Gynecol, 120 (2012) 104.

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ULOGA ANTIBIOTSKE PROFILAKSE U PRERANOM PRIJEVREMENOM PRSNUĆU VODNJAKA

SAŽETAK

Prerano prijevremeno prsnuće vodenjaka (PRVP) javlja se u 3% svih trudnoća i odgovorno je za, ili je povezano sa približno jednom trećinom prijevremeno rođene djece uzrokujući značajni perinatalni morbiditet i smrt fetusa. Nedonoščad su vrlo osjetljiva na respiratorni distresni sindrom (RDS), intraventrikularno krvarenje (IVK), periventrikularnu leukomalaciju (PVL) te druge neurološke bolesti, infekcije i nekrotizirajući enterokolitis (NEC). Korioamnionitis se na temelju kliničkih kriterija javlja u oko 3-30% svih trudnoća kompliciranih PRVP-om. Cilj ovog istraživanja bio je analizirati ulogu antibiotske profilakse za konačni neontalni ishod (tjelesnu težinu, Apgar ocjenu, plućne komplikacije, neurološke komplikacije – abnormalni moždani ultrazvučni pregled prije otpusta iz bolnice, perinatalne infekcije) i utvrditi mogućnosti optimalanog antibiotskog liječenja. Stoga smo retrospektivno analizirali trudnoće kompliciranе PRVP-om u posljednjih 5 godina u našoj ustanovi, te učinili pregled kliničkog tijeka i ishoda tih trudnoća liječenih profilaktičkim antibioticima i kortikosteroidima. Ukupno je bilo 324 nedonoščadi iz trudnoća koje su ispunile kriterije za uključenje u naše istraživanje, 190 u studijskoj grupi (trudnica je dobila empirijski antibiotik) i 134 u kontrolnoj skupini (bez antibiotika). Pronašli smo značajnu razliku u gestacijskoj dobi ($p<0,0001$), porođajnoj težini ($p<0,0001$), Apgar ocjeni ($p<0,0001$), vrijednostima majčinog C-reaktivnog proteina ($p<0,0001$) i razdoblju latencije (5,54 dana *vs.* 11.33days, $p=0,001$) između skupina. Histološki korioamnionitis je znatno češći u studijskoj skupini (14,2% *vs.* 36,3%, $p<0,0001$). Pronašli smo značajnu razliku u ishodima novorođenčeta s obzirom na različitu antibiotsku profilaksu. Antenatalna antibiotska i kortikosteroidna terapija imaju jasne prednosti i trebaju biti ponuđene svim ženama u trudnoćama kompliciranim PRVP-om ukoliko nema kontraindikacija za njihovu primjenu.