ANTENATAL CORTICOSTEROID THERAPY IN MANAGEMENT OF PRETERM LABOR CAUSED BY PRETERM PREMATURE RUPTURE OF MEMBRANES - RISKS AND BENEFITS

Tondys-Kohmann Ewa¹, Zareba-Szczudlik Julia², Romejko-Wolniewicz Ewa²

1. Princess Anna Mazowiecka Hospital in Warsaw, Poland
2. 2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

#Corresponding author: Julia Zareba-Szczudlik, e-mail: juliaszmed@wp.pl, Warsaw Medical University, Karowa St 2, p. o. box 00-315 Warsaw, Poland, phone number +48 22 5966 421, fax +48 22 5966 487

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ABSTRACT

Preterm labor is a common complication of pregnancy, in one third of the cases it is caused by preterm premature rupture of membranes (PPROM). Since the crucial article by Liggins and Howie published in 1972, antenatal corticosteroid therapy has played a prominent role in the management of preterm labor. Nowadays plenty of studies have shown the effectiveness of the therapy in reducing neonatal mortality and morbidity. However, there is some ambiguity about the therapy in certain cases, including PPROM. The immunosuppressive activity of steroids is widely known. Even though the corticosteroids generally used in the management of preterm labor (betamethasone, dexamethasone) show very weak immunosuppressive activity, there is still some doubt regarding the possible increase in risk of neonatal and maternal infection. Other questions concern the effectiveness of the therapy in this group of patients, as well as current recommendation of main obstetricians’ societies and safety of use of repeated doses. The aim of this article is to highlight the latest knowledge in this area.
PPROM (preterm premature rupture of membranes) is a common complication of pregnancy which occurs in 1-2% of cases [1, 2, 3, 4]. PPROM is also known to be the most significant cause of preterm births (30-40%) [1, 2, 3, 4]. Besides all short- and long-term complications of prematurity including intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), cerebral palsy, visual and hearing impairment, learning disabilities and behavioral issues. PPROM can also lead to neonatal sepsis, which affects up to 20% of these neonates [1, 5]. Since the crucial article by Liggins and Howie published in 1972 and the National Institutes of Health (NIH) Consensus in 1994 a great role in the management of preterm labor is played by antenatal corticosteroid therapy, which is known to reduce numerous complications of prematurity, such as RDS or IVH [5, 6].

There is concern about using corticosteroids in pregnant women with premature rupture of membranes due to the possible increased risk of neonatal and maternal infection [7, 8, 9, 10, 11, 12]. The aim of this article is to highlight the current knowledge in this area.

DO ANTENATAL STEROIDS IN THE MANAGEMENT OF PRETERM LABOR CAUSED BY PPROM INCREASE THE RISK OF NEONATAL INFECTION?

A review recently prepared for publication entitled "Use of antenatal corticosteroids in special circumstances: a comprehensive review" [13] compared 17 controlled trials questioning the influence of admission of prenatal steroids in PPROM pregnancies on incidence of neonatal sepsis. Authors analyzed data in 2 groups - pregnancies complicated with PPROM in which women received steroids and in which they did not. There was no significant difference between study and control groups in the risk of neonatal sepsis. Other studies also confirm the statement that admission of one course of antenatal steroids in PPROM-complicated pregnancies does not increase the risk of neonatal sepsis [7, 14, 15].

DO ANTENATAL STEROIDS IN THE MANAGEMENT OF PRETERM LABOR CAUSED BY PPROM INCREASE THE RISK OF MATERNAL INFECTION?

The latest Cochrane Systematic Review compared pregnancies complicated with PPROM treated with one course of corticosteroid to those without this treatment [7]. No statistically significant differences were seen for maternal death, chorioamnionitis or puerperal sepsis [4]. This statement is reiterated in numerous reviews and studies [13, 14, 15, 16].

DO ANTENATAL STEROIDS IN MANAGEMENT OF PRETERM LABOR CAUSED BY PPROM DECREASE THE RISK OF COMPLICATIONS OF PREMATURENESS?

The same Cochrane Review as previously [7] reports a statistically significant decrease in the risk of the following complications of prematurity for infants whose mothers underwent antenatal steroid treatment in course of the management of preterm labor caused by PPROM:

1. combined fetal and neonatal death (RR 0.62, 95% CI 0.46-0.82)
2. RDS (RR 0.67, 95% CI 0.55-0.82)
3. IVH (RR 0.47, 95% CI 0.28-0.79)
4. chronic lung disease (RR 0.50, 95% CI 0.33-0.76)
5. NEC (RR 0.39, 95% CI 0.18-0.86)
6. duration of mechanical ventilation or continuous positive airway pressure - CPAP but not for mechanical ventilation or CPAP (RR 0.90, 0.47-1.73) [4].

In the opposite, the latest review [13], mentioned before, confirms only the reduction of risk in RDS (RR 0.81, 95% CI 0.67-0.98), IVH (RR 0.52, 95% CI 0.37-0.72) and severe IVH (grade III and IV, RR 0.49, 95% CI 0.25-0.96), but not in NEC, neonatal sepsis, Apgar score <7 at 5 minute, perinatal/neonatal mortality [13].

The American College of Obstetricians and Gynecologists (ACOG) confirm the statement for neonatal mortality, RDS, IVH and NEC [16, 17, 18]. Additionally, a meta-analysis of observational studies demonstrated corticosteroids were effective in reducing neonatal morbidity/mortality (IVH - grade III, IV, and periventricular leukomalacia), even if histologic or clinical chorioamnionitis developed after treatment started [19].

IS THERE SUFFICIENT DATA TO RECOMMEND ANTENATAL CORTICOSTEROIDS FOR WOMEN AT RISK OF PRETERM BIRTH DUE TO PPROM?

The American College of Obstetricians and Gynecologists (ACOG) recommend a single course of corticosteroids for pregnant women with PPROM between 24 0/7 weeks and 33 6/7 weeks of gestation and also as an option to consider for those at 23 0/7 weeks of gestation and at risk of preterm delivery within 7 days [16]. Also Royal College of Obstetricians and Gynecologists accept this recommendations [6].

WHAT ABOUT MULTIPLE COURSES OR A RESCUE DOSE?

For the same reason of potential infectious complications, for which antenatal corticosteroid therapy was initially controversial in PPROM cases, the safety and benefits of use of one rescue dose or multiple repeated courses in these patients remain unclear. The Cochrane Review 2015 found only one trial [20] which analyzed a subgroup of women with PPROM, comparing single versus weekly courses of antenatal corticosteroids [21]. There was no statistically significant difference in occurrence of complications of prematurity such as RDS, fetal/ neonatal/ infant death and chronic lung disease, between study and control group [20, 21]. However, treatment with repeated doses was associated with an increased risk of chorioamnionitis (RR 1.56, 95% CI 1.05 to 2.31) although no differences were seen for puerperal sepsis between the groups (RR 0.65, 95% CI 0.19 to 2.22) [20, 21]. Also, older studies find some danger in multiple courses in PPROM-cases, including increased
risk of early-onset neonatal sepsis, chorioamnionitis and endometritis [14].

Not many data can be received about a single rescue course. Only one study published in 2014, compared standard course versus one rescue course of corticosteroids in patients with PPROM [22]. They found no statistically significant difference in the incidence of chorioamnionitis between the groups, ever after accounting for other obstetric and perinatal covariates (RR 0.87, 95% CI 0.54,1.42, p = 0.292) [19].

In the opinion of ACOG Committee 2016 whether to administer a rescue course of corticosteroids in pregnancies complicated with PPROM is controversial and there is no sufficient data to make a recommendation for or against [16].

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ABBREVIATIONS

PPROM – preterm premature rupture of membranes
IVH – intraventricular hemorrhage
NEC – necrotizing enterocolitis
ROP – retinopathy of prematurity
PDA – patent ductus arteriosus
NIH – National Institute of Health
CPAP – continuous positive airway pressure
RR – risk ratio
CI – confidence interval
ACOG – American College of Obstetricians and Gynecologists

REFERENCES


