USE OF CORTICOSTEROIDS TO PREVENT COMPLICATIONS IN PRETERM BIRTH

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Abstract. Preterm birth is a medical and severe socioeconomic problem. It is the most common cause of neonatal mortality in developed countries represents 80% of all deaths worldwide in neonatology (over 1.1 million) and more than 30% of the same in Europe. In the United States as of 2010 over 12% of all births are preterm, where 30% increase is observed since 1981 till the present moment. In Brazil, the rate is about 6.5% in 2006 and it is growing, reaching 10.7% in 2011. In prenatal and neonatal medicine, newer and customizable preventive measures are applied in order to reduce the risk of death of preterm infants, and reduce the probability of developing health complications and drug-related side-effects in the treated women and newborns. The positive aspect of corticosteroid use is the aim to achieve preventive effect on respiratory distress syndrome, hyaline membrane disease (HMD) and other complications, as from a medical point of view this is a much preferred preventive approach.

The purpose of corticosteroid effective prevention is to reduce complications in prenatal infants and shorten their stay in the neonatal and intensive care units, which in itself is extremely serious socio-economic problem.

Key words: corticosteroids, dexamethasone, preterm birth, prevention, HMD.

Introduction

As preterm (premature) is classified the birth of a viable infant, weighing less than 2500g, before 37 gestational week of the pregnancy [2, 4, 6, 34, 62]. For a newborn infant weighing less than 1500g, the probability to exit soon after his or her birth is 200 times greater than that of a full term infant [2]. Typical anatomo-physiological characteristics of the preterm infant are: weight within 500g and 2500g; height of 35-45 cm; appearance of an old man; reduced muscular tone; incorrect and shallow breathing; quiet crying due to undeveloped (unexpanded) lungs; dry livid skin, with reduced turgor; transparent blood vessels; open occipital fontanelle; underdeveloped nails; underdeveloped descensus testiculorum, etc. [1]

Preterm birth is characterized by complex and unclear etiology. A specific reason for preterm birth cannot be defined, however a combination of etiologic factors are discussed as such increasing the risk rate. Three main groups of etiologic factors are examined: socioeconomic, medicobiological and behavioural.

The consequences of preterm birth include a number of medicobiological and socioeconomic adversities. The research work of Petrou S. et al. analyzes the complex of negative aspects arising from preterm birth, respectively during the first 5 (2001) and 10 (2005) years of the lives of preterm infants. [48, 49, 50] The authors make the conclusion that cerebral paralysis occurs with a higher rate in preterm born children, compared to full term infants. The first group shows also
higher rate of permanent complications arising from respiratory diseases and sensory deficiencies. The increased morbidity related to preterm birth affects the individual at a later age too. This leads to considerable physical disorders of various scope, emotionally and psychologically negative consequences and substantial socioeconomic costs both for the family and for the society generally.

For the reduction of preterm birth incidence the adequate and specialized prenatal cares are of considerable importance. These have to be customized and to take into account the complex of risk dispositions of each individual case of pregnancy. [32, 35]

The development of the lungs does not occur normally in all newborn infants. Every year approximately 15 million preterm infants are born in the world. [4] One of the pathological syndromes of the preterm infants is related exactly to the development of the lungs and it is denoted as hyaline membrane disease (HMD). It is caused by insufficiency of surfactant synthesis in combination with structural immaturity of the lungs. It is possible also to be caused by a neonatal infection. [60, 61] The hyaline membrane disease affects 1% of the preterm infants globally, and it is the main reason for death cases in this group of patients. [56]

**Exposure**

In the period 2007-2009 in several countries of Central and Eastern Europe has done extensive research related to preterm birth. [12] It involved six medical centers in Czech Republic (University Hospital, Hradec Kralove), Hungary (Budapest, Semmelweis University; and Pecs, Medical School, University of Pecs, a regional tertiary center for preterm birth), Romania (Carol Davila University of Medicine and Pharmacy), Slovakia (Slovak Medical University Hospital) and Ukraine (Danylo Halytskyy Lviv National Medical University). They were examined socio-economic factors such as smoking, drug use and disease (by 46 indicators), problems and interventions during the pregnancy (27 indicators). There were conducted specialized tests and measurements, used a progesterone, analyzed 21 indicators. Of a total of 37,661 births, 90% were on time and 10% were premature. The average rate of premature birth is 10.27%. The average age of mothers with normal pregnancy was 28.54 ± 5.39 years, while that of women with preterm birth was 29.30 ± 5.93 years.

In the study the link between premature birth and each predictor is initially analyzed by single factor logistic analysis to establish its influence statistically significant. For Romania, none of the risk factors indicates a significant impact on prenatal birth and for indicators of the country are not included in the multi-criteria analysis logistics.

Low body mass index as a predictor of preterm birth is found for the Czech Republic ($P <0.0001$), Slovakia ($P <0.040$) and Ukraine ($P <0.001$). The analysis shows that tobacco (duration of smoking and current smoking) have a major influence on the incidence of prematurity in 4 center - Czech Republic, Hungary (Budapest and Pecs) and Ukraine ($P <0.0001$ respectively for each center), with the exception of this depending make Romania ($p = 0.230$) and Slovakia ($p = 0.140$ for the duration of smoking and $p = 0.100$ for current smokers). This is the predictor that displays the greatest impact on preterm birth of negative factors examined in the study. Duration of diabetes and the presence of diabetes (incl. Gestational) do not appear in any predictors center, with the exception of Pecs (Hungary) ($p = 0.000$ for the duration of diabetes). Hypertension as a risk factor has a significant impact on premature birth only in data from Slovakia and Ukraine ($p = 0.001$ respectively for each center). In 4 of centers is found that the presence of preeclampsia (Hungary, Ukraine and Slovakia) materially affect the duration of pregnancy. The use of hormonal drugs, such as progesterone, predicts preterm birth in the Czech Republic, Hungary (Budapest) and in Ukraine. Anemia and use of medications containing iron have been identified as risk factors for premature birth in three of the monitored centers. The survey data shows that in Ukraine are considered the most statistically significant predictors of premature birth - 7 out of 10 surveyed. Exceptions are the presence of diabetes, duration of diabetes and BMI. [12]
The opinions of a number of authors regarding the various factors increasing or respectively reducing the risk of HMD development agree. In medical literature these factors most often are systemized in the following two groups: 1. The factors increasing the risk of HMD development are: male sex of the foetus; perinatal asphyxia; birth by caesarian section; diabetes of the mother; multiple pregnancy; preterm birth (before 28 g.w.); hypothermia; previous child with HMD. [44] And 2. The factors reducing the risk of HMD are: chronic fetal distress; amnionitis; treatment of the mother with corticosteroids and tocolytics; intrauterine hypotrophy of the foetus; continuous anhydrous period, i.e. premature puncture of the amniotic sac (exceeding 18 hours). [36, 37, 3]

The clinical expression of the hyaline membrane disease occurs either immediately after birth or within 6 hours after it. The symptoms observed in a newborn infant with HMD are the following: tachypnea – unusual rapid breathing – a medical symptom of pneumonia; expiratory groaning; epigastric and intercostal sinking; nostril breathing; cyanosis – appearance of bluish or livid colour on the skin or mucosa, which results from the fact that the tissues located near the skin surface receive less oxygen saturation; [41, 42] apnea and/or hypothermia may occur. [7]

The hyaline membrane disease is often accompanied by additional complications. They are classified in two main groups, respectively early (acute), and later (chronic) complications. The early ones include: pulmonary edema; infection; intracranial hemorrhage and periventricular leukomalacia; apnea; pulmonary hemorrhage; necrotizing enterocolitis and/or gastrointestinal perforation. The later complications consist of: bronchopulmonary dysplasia; retinopathy; neurological disorders. [24]

In a study conducted during the period between 1969 and 1972 Liggins G. and Howie R. found out that if pregnant women threatened by preterm birth were prescribed corticosteroids, then the chance their newborn to develop respiratory distress syndrome was reduced considerably. They applied ether betamethasone phosphate or betamethasone acetate. This study, as well as on the basis of its results changed the method of treatment applied by the doctors in the cases of existing risk of giving birth between 24 and 36 gestational week, in order to improve the quality of life of the preterm infants. [38]

The respiratory distress syndrome is the most frequent cause for the death of preterm infants. [33] Even those who survive are characterized with a high risk of development of cerebral paralysis, subsequent problems during the educational process, and respiratory disorders. [59] Statistics show that in the countries with high income the percentage of preterm births varies between 7% and 12%, while in the countries with low and medium income, as for example the countries in Africa, it can reach 20%. In October 2010 various international organizations held a meeting in Washington with the aim officially to discuss the evidence on the benefits from prescribing prenatal corticosteroids in the countries with low, medium and high income.

On the basis of the information from studies in the high income countries it is found out that prenatal corticosteroids are effective for reducing the percentage of neonatal death rate of newborn infants between 24 and 34 gestational week. The results from the meta-analysis of 21 clinical researches confirm this fact, and also notes that this drug profiling reduces the risk of HMD development by newborn infants from all races and from the two sexes at the age from 31 to 34 gestational week. It emphasizes on the possibility the prenatal corticosteroids to be effective also at age before 31 and after 34 gestational week. It is also found out that the use of prenatal corticosteroids does not cause infections in the mother or the foetus. [15, 40, 45] Here arises the question which corticosteroid is more efficient. [63] Several studies show that betamethasone can be more effective than dexamethasone. The main reason for expressing such an opinion is the greater probability betamethasone to cause less side effects on the mother. Also, the used suspension of betamethasone phosphate and betamethasone acetate is a better combined variant than other betamethasone preparations. [55] In countries with low and middle incomes, several studies have shown significant differences in the application of prenatal corticosteroids.
In the countries of Southeast Asia the percent of prescribed drugs ranged from 9% to 73%, separately inside the countries themselves percent is with values between hospitals from 0% to 86%. [42] Although the benefits of betamethasone and dexamethasone has been shown, many pregnant women in Africa have no access to them and those who are less than 5%. [57] On the one hand this is due to lack of medicines in hospitals and on the other they are only limited availability in neonatal wards. [19] That reaches to the conclusion that prenatal corticosteroids effectively reduce neonatal mortality and respiratory distress syndrome associated with premature birth (at 24-34 gest. week). [21] There were four studies in hospitals in middle-income countries, respectively, Brazil, South Africa, Tunisia and Jordan, which offers neonatal care. In Brazil and Tunisia was administered betamethasone, while in South Africa and Jordan, the choice is stopped on dekasametazon at risk of developing respiratory distress syndrome. [24, 46, 51, 57] As a result of the studies it was found that the efficacy of corticosteroid treatment in middle-income countries is similar to that of high income countries. The rate of neonatal mortality in middle-income countries is higher than in high income countries, so marks and a big drop in the poorer countries.

Aleman A. et al. (2013) conducted a study on the use of antenatal corticosteroids in Latin America. The study involved research centers in Mexico, El Salvador, Uruguay and Ecuador. The aim is to evaluate the knowledge, attitudes and practices in the delivery of health services related to the use of prenatal corticosteroids for women at risk of premature birth in these areas. Socio-demographic characteristics of the study participants are shown in Table 1.

The study involved 353 medical specialists. The degree of drug response was 98% (59/60) in Mexico (Zelaya), 96% (109/113) in El Salvador, 65% (121/186) in Uruguay and 48% (64/133) in Ecuador. They report on the prescription of prenatal corticosteroids as demonstrated on Table 2. [6]

Prenatal corticosteroids prescribed to women in risk of giving premature birth are proven to reduce the danger of development of intraventricular hemorrhage and respiratory distress syndrome, as well as the neonatal death rate with 50%, and in some cases with 60% and more. [16, 45, 58]

Considerable variance exists in the literature regarding the distribution and use of prenatal corticosteroids in the countries in Latin America; there are few published studies and the posi-

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<th>Table 1. Socio-demographic characteristics of the study participants in Latin America</th>
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The efficacy of the prenatal corticosteroid treatment depends to greatest extent from the gestational age. In his research, Mori R et al. (2011) assesses the effectiveness of this treatment among 11 067 patients, whose gestational age was between 22 and 33 week. On the basis of the obtained results from the research, a conclusion is made that prenatal steroids reduce the risk of respiratory distress syndrome development by 9%. More substantial is here the ascertained fact that the treatment effectiveness is higher in newborn infants between 24 and 29 gestational week, as for them the risk of respiratory distress syndrome development is reduced with 20%. [43]

Contrary to previous studies, researching Gyamfi-Bannerman C. et al., (2012) evaluated the effect of the administration of antenatal corticosteroids before caesarean section as compared to women who were not prescribed such drugs. The aim is to determine whether the newborns whose mothers received corticosteroid treatment course, have fewer health disorders compared to those whose mothers were given antenatal corticosteroids.

The authors found that compared to neonates of no treated women, newborns of those who received corticosteroids are more likely to develop respiratory distress (17.1% versus 12.2%, p = 0.001), transient tachypnea (12, 9% to 9.8%, p = 0.020), need assistance with breathing (11.5% vs. 8.6%, p = 0.022), need for resuscitation in the delivery room (55.8% to 49.7% , p = 0.007). After adjusting for these confounding factors, they found that there are no significant differences between groups in terms of all of the above results with odds of respiratory distress 0.78 (95% CI 0.60-1.02) and mechanical ventilation 0.75 (95% CI 0.55-1.03) . They conclude that exposure to antenatal corticosteroids has no significant effect on the development of lung disorders in later births. [18]

Porto AM et al. (2011) found that corticosteroid treatment prescribed to women in 34 to 36 gestation weeks did not show the expected effect, does not reduce the incidence of respiratory distress in infants. [51]

Kamath-Rayne BD et al. (2012) also confirm that drug treatment conducted after the diagnosis of fetal lung immaturity, has not necessary effect on newborns in 34 or later than her gestational age, not reduces the incidence of respiratory system. [33]

Now for 30 years, glucocorticoids have been used in the medical practice in the event of risk of preterm birth, so that the foetus is provided with enough time in order his or her lungs to develop to the required degree. Also, they have led to the reduction of HMD incidence, ventricular hemorrhages in the preterm infants, the neonatal morbidity and death rate with about 50%. [23]

There is evidence that uncompleted treatment with betamethasone or dexamethasone provides some advantages with regards to reducing the morbidity of preterm infants. These advantages most probably are due to prescribed unsuitable

<table>
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<th>Start of corticosteroid prescription</th>
<th>El Salvador (N=109)</th>
<th>Mexico (N=59)</th>
<th>Ecuador (N=64)</th>
<th>Uruguay (N=121)</th>
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<tr>
<td>Before 24 g.w.</td>
<td>n/N (102) [0.0-5.3]</td>
<td>n/N (41) [9.8]</td>
<td>n/N (60) [2.7-23.1]</td>
<td>n/N (101) [0.0-5.4]</td>
</tr>
<tr>
<td>24-27 g.w.</td>
<td>n/N (52) [40.9-61.0]</td>
<td>n/N (8) [19.5]</td>
<td>n/N (21) [35.0]</td>
<td>n/N (81) [80.2]</td>
</tr>
<tr>
<td>28-34 g.w.</td>
<td>n/N (49) [38.0-58.2]</td>
<td>n/N (29) [70.7]</td>
<td>n/N (39) [65.0]</td>
<td>n/N (19) [18.8]</td>
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dosages of the drugs or a shorter therapy course, during which the foetus is exposed less to the effect of the steroids. [21]

According to recommendations by doctors from Great Britain, prenatal steroid treatment may be repeated before 34 week of the pregnancy, if the first treatment was completed 7 days before 26 gestational week. [58] Crowther et al. (2011) summarizes the results from 8 researches concerning the repeated steroid treatment after a 7 days’ interval. On the basis of the collected data the conclusion is made that the respiratory distress syndrome occurs less frequently in newborns with applied second treatment, relative risk RR=0.83 (95% CI 0.75-0.91). [17]

It is assumed that the application of more than two corticosteroid therapy courses could lead to more serious consequences on the subsequent development of the newborn. French NP et al. (1999) proves that the serial steroid therapies applied between 24 and 33 gestational week reduce the weight at birth, as well as the head circumference. [27]

A study by Atarod Z. et al (2014) compares the prenatal application of single and multiple therapy courses with betamethasone, as well as its efficacy, and to what extent it is safe for the mother, to use several consecutive treatments with this drug. According to the obtained results the multiple course with betamethasone has positive effect for the reduction of infants’ death rate and morbidity, but before it is proven that they are safe for the newborn, their application is not recommended. [66]

Chien et al. (2002) provides data about the prenatal steroid treatment of 11 440 newborn infants. In this study, in only 30% of the cases of newborns the medication treatment course was completed. The data shows that exactly these 30% demonstrate considerable reduction of the probability of developing respiratory distress syndrome, but only when they have been born between 24 and 34 gestational week. These newborn infants who received incomplete therapy course do not show major difference in the chance of developing respiratory distress syndrome compared to the ones who received the full course. [13]

According to the current standard of practice, women exposed to risk of preterm delivery during 24-34 gestational week of the pregnancy, are subjected to corticosteroid treatment. Both medications can be used for the treatment depending on the opinion of the attending physician: 1. Two doses of 12 mg betamethasone are applied at a 24-hour interval; or 2. Four doses of 6 mg dexamethasone are administered intramuscularly at intervals of 12 hours. [5, 17]

Although dexamethasone is characterized with its greater affinity to the glucocorticoid receptors, betamethasone has longer semi-life which gives it advantage and makes it preferred in the medical practice. In almost identical ways both steroids reduce the risk of perinatal death. [11]

A research by Romejko-Wolniewicz E. et al. (2014) raises the question whether it is necessary to optimize the corticosteroid doses. The authors reach the conclusion that:

1. A total dosage of 24 mg of betamethasone or dexamethasone is enough to achieve the necessary steroid concentration in the newborn.

2. Administering of 12 ml betamethasone at shorter intervals allows for conducting a complete treatment course.

3. The lower single dose of 4 or 6 mg is as much effective as the 12-mg dose, differing only in that it is less toxic for the mother. This allows for reducing the treatment side effects on the mother.

4. In a multiple pregnancy there is no need to increase the dosage of 24 mg.

The short-term and long-term effects of the dosage plans, both on the mother and on the foetus require further and more thorough research. [57]

Conclusion

On the grounds of the analyzed data, several statements can be drawn regarding the benefits and negative effects of the use of corticosteroids for the prevention of complications in newborn infants in cases of pregnant women with actual risk of preterm birth. Some researchers do not find considerable preventive and therapeutic effect, however the opinions
of most authors support the beneficial effect of the dexamethasone prevention. Prophylaxis with corticosteroids eases the financial burden on families with premature infants to hospitals. It allows a larger number of patients may benefit from therapy and is more profitable economically for neonatal wards.

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