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Original Research

A comparative study of the contribution of antenatal corticosteroids administration on improving neonatal respiratory function after elective cesarean section

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Summary

Objective: The purpose of this study was to investigate the effect of corticosteroid administration (CA) 48 hours before an elective cesarean sections (ECS) at term neonates, as compared to usual management without corticosteroids, as well as antenatal CA is related to reducing neonatal respiratory problems (RP). *Materials and Methods:* A retrospective study was conducted in neonates who were born between 37 and 39 gestational weeks after ECS and 718 pregnant women at term, who underwent ECS were enrolled. The participants were categorized in two groups. Group 1 consisted of 315 pregnant women who underwent CA (a single dose of 12 mg betamethasone (BS) 48 hours before the ECS). Group 2 consisted of 403 pregnancies, that did not receive any BS before the ECS. *Results:* There were no significant differences ($p > 0.05$) in APGAR scores, at one and five minutes between the two groups. Nineteen (2.6%) children were born with respiratory problems. The incidence of RP was significantly higher ($p < 0.05$) in women who did not receive corticosteroids in contrast to those who received them (3.7% *vs.* 1.3%). In group 2, the lack of CA was associated with a three-fold increase in risk of RP in neonates (OR: 3.01). In group 2 an increased risk of RP in neonates was observed during 37 or 39 weeks (40% and 75%, respectively), but these trends were not statistically significant. *Conclusion:* The single-dose of prenatal administration of (BS) 48 hours before the ECS, seems to improve the lung function of neonates.

Key words: Corticosteroid administration; Elective cesarean section; Term pregnancies**.**

Introduction

Antenatal corticosteroid treatment has been reviewed in randomized or controlled trials only in relation to spontaneous preterm labor or premature rupture of the membranes [1]. It is already known that the administration of corticosteroids to pregnant women before labor, helps in the prevention of respiratory distress syndrome (RDS), promotes the appearance of surfactant, reduces the risk of intracerebral hemorrhage, necrotizing enterocolitis, open ductus arteriosusous, acceleration of the kidney, skin maturation, and mortality in preterm neonates [2-6]. Moreover, the use of corticosteroids has been found to contribute in better cardiovascular responses, such as secretion of peptides in premature neonates in both the fetal (increased gastrin) and postnatal periods (increased motilin).

Synthetic steroids are administered to pregnant women with congenital adrenal hyperplasia. The treatment is offered in early pregnancy and in some cases during the entire pregnancy. Beta-methazone administration seems to be important in congenital diaphragmatic hernia [7-9].

The transition from a lung filled with fluid in a lung full of air is the greatest challenge facing a newborn immediately after birth [10]. The success of corticosteroid injection in pregnant women to accelerate fetal lung maturation prior to preterm labor led to evaluate this medication in elective cesarean sections at term of gestation. Prenatal injection of steroids may improve postnatal lung function leading to enhance of gas exchange, compliance, oxygenation, and resulting in fewer ventilator days and lower oxygen requirements [11].

Based on the guidelines of the National Institute for Clinical Excellence which recommend that alone a women's request is not included in medical indications for performance of cesarean section, an elective cesarean section (ECS) at term pregnancies and especially the consequences for the neonates, received little attention in the past [4, 12]. However, in the last years the rate of planning ECS without medical indications was increased depending on social reasons, possible the older age of conceptions, changing management according to previous CS, and breech presentation [4].

RDS and transient tachypnea of the newborn (TTN) may

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occur independently of pregnancy week and delivery modus. Although the risks of a vaginal delivery, such as perinatal asphyxia, trauma to the neonate and the meconium aspiration are reduced, an ECS as only independent risk factor leads to a two- to four-fold increase in the risk of RDS, TTN, deficiency of surfactant, necessity for mechanical ventilation, asthma, type 1 diabetes mellitus, and atopy compared to intended vaginal delivery [4, 13-15]. Vaginal labor causes a sharp increase of endogenous corticosteroids and catecholamines, which accelerates the absorption of fetal lung liquid and stimulates the release of surfactant [16]. The antenatal corticosteroids administration triggers this mechanism and is useful for neonates with a gestational age greater than 34 weeks, especially for those who will be born by an ECS without the start of a vaginal labor. Studies have shown the presence of significantly lower levels of catecholamines and changes in lung function of full-term newborns who were born by an ECS, compared with infants born vaginally [13]. The observed benefit of antenatal corticosteroids is greater 24 hours after administration, with maximum effect after 48 hours [5]. Their beneficial effect seems to be reduced seven days after injection, but their effect on the architecture of the alveoli remains positive [17]. The most common used antenatal corticosteroids are betamethasone and dexamethasone. They cross the placenta in sufficient quantities, and they present mainly glucocorticoid and less alatocorticoid activity. The purpose of this study is to assess if the injection of single dose of 12 mg betamethasone 48 hours before an ECS can improve the respiratory function of and decrease the admission to neonatal intensive care unit (NICU) and complications from invasive procedures.

Materials and Methods

A retrospective study was conducted in neonates who were born after ECS between 2003 and 2006 at the Department of Obstetrics and Gynecology in the University of Thrace. The participants of the study were all pregnant women, who underwent to an elective cesarean section between 37 and 39 gestational weeks. The authors categorized the pregnant women in two groups. Group 1 consisted of 315 (43.9%) pregnant women and a single dose of 12 mg BS was injected to the women of this group, 48 hours before the ECS. In Group 2, 403 (56.1%) pregnant women who did not receive any BS before the ECS were included. The decision to give corticosteroids was arbitrary. All pregnant women were informed about the use of corticosteroids. Those who eventually received them, gave written consent. All pregnant cases were uncomplicated singleton, cephalic, and term pregnancies. Pregnancies with serious obstetric or medical complications, like severe maternal hypertension, evidence of intrauterine infection, regional anaesthesia, either spinal anaesthesia (SA) or epidural anaesthesia (EA) techniques, and none of them have received general anaesthesia. The following parameters about pregnant women and newborns were evaluated and compared between two groups. The Apgar score at one and five minutes, the birth weight among newborns, the assessment of the severity of neonatal respiratory morbidity depending on the admission in NICU, the duration of hospitalization, and complications in the NICU were evaluated.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 13.0. The normality of continuous variables was tested with Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as the mean ± standard deviation, while non-normally distributed variables were expressed as the median and range. Categorical variables were expressed as frequencies and percentages. Student's *t*-test or Mann-Whitney U-test was used to determine differences of demographic and clinical characteristics between the two groups of women according to the corticosteroids administration. The chi-square test was used to evaluate any potential association between categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by means of simple logistic regression analysis as the measure of association between respiratory problems and corticosteroids administration 48 hours before the ECS. All tests were two-tailed and statistical significance was considered for p values less than 0.05.

Results

During a three-year period there were identified 718 singleton uncomplicated pregnancies at term which underwent an ECS. The demographic and clinical characteristics of these women are summarized in Table 1. The age of the women was 30.17 ± 5.43 (mean ± SD) (range 17-45) years. There were no significant differences in mother's age (p = 0.306), child's weight (p = 0.121), gestation week (p = 0.246), and APGAR scores, at one (p = 0.568) and five (p = 0.654) minutes between the two groups of women. The APGAR scores were assessed by a neonatologist. The diagnosis of respiratory morbidity included RDS and TTN, depending on clinical symptoms, like tachypnea (more than 60 breaths per minute, nasal flaring, and cyanosis). Chest radiological findings included radiological features of transient tachypnea of the newborn or the reticular glandular pattern of RDS.

Among the entire cohort, 19 (2.6%) neonates were born with acute respiratory disorders and were admitted to the NICU, 16 of them for transient tachypnea (TT) and three for RDS. From the newborns with the respiratory problems, 14 (12 with TT and two with RDS) were delivered from pregnant participants of group 2 (Table 2). The incidence of problems was significantly higher among women who did not receive corticosteroids compared to those who received them [15 (3.7%) *vs.* 4 (1.3%)] (p = 0.033) (Table 2). In logistic regression analysis, the lack of corticosteroids injection was associated with a three-fold increase in risk of respiratory problems (OR, 3.01; 95% CI, 1.00-9.15; p = 0.050) (Table 2). When the authors stratified the analysis according to gestation week, they observed that the beneficial effect of corticosteroids injection appeared more pronounced during the 38th week than during the 37th or 39th week. In this regards, the lack of corticosteroids administration yielded an OR of respiratory problems of the newborn of 7.20 (95% CI = 1.01–56.84, p = 0.050) during the 38th week (Table 2). Among women with lack of corticosteroids injection, increased risk of respiratory problems was

Table 1. Demographic and clinical characteristics of women of the study

	Group 2	Group 1	P value
Number of women%	403	315	
Age (years)			0.306
Mean ± SD	30.35 ± 5.34	29.94 ± 5.53	
Range	18 – 45	17 – 41	
Gestation week [no (%)]			0.246
37th	63 (15.6)	58 (18.4)	
38th	217 (53.8)	150 (47.6)	
39th	123 (30.6)	107 (34.0)	
Weight (gr; mean ± SD)	3180.97 ± 379.64	3230.44 ± 455.33	0.121
APGAR at 1 min			
Mean ± SD	8.90 ± 0.57	8.92 ± 0.48	0.589
Median (range)	9 (4-9)	9 (5 -10)	0.568
≤7 [no (%)]	8 (2.0)	6 (1.9)	0.938
APGAR at 5 min			
Mean ± SD	9.93 ± 0.42	9.94 ± 0.40	0.910
Median (range)	10 (5 – 10)	10 (6 – 10)	0.654
≤7 [no (%)]	5 (1.2)	3 (1.0)	0.715

also found during the 37th or 39th week, by 40% and 75%, respectively (Table 2). However, these trends were not statistically significant (OR = 1.40, 95% CI= 0.23–8.69, p = 0.718 for 37th week; OR = 1.75, 95% CI = 0.16–19.60, p = 0.649 for 39th week) (Table 2) Infants who did not receive antenatal corticosteroids and appeared with respiratory problems, usually developed TT or RDS (especially in neonates of 37th gestation week). The treatment of neonates in the NICUs, relates the need for mechanical ventilation, by referring mainly for the use of continuous positive airway pressure masks (CPAP) for two to three days and then they are treated by using diffused oxygen. The residence in the intensive care units was about seven to ten days and it also depended on the results of the blood culture and the response of the neonates to the antibiotic treatment.

Term neonates who did not receive antenatal corticosteroids and apparent respiratory problems, even if they presented RDS, responded better to treatment with oxygen, usually in two to three days, and they left the NICU in less than seven days.

Neonates who received antenatal corticosteroids when they presented respiratory problem usually developed TT but they responded more easily to treatment with oxygen and they usually left in five days from the NICU.

Discussion

The frequency of ECS in the Western countries has increased significantly over the last three decades [18]. In the United Kingdom, in 1995, the percentage of ECS was 16%, while in 2007 it rose to 25% [19-20]. In the USA, in 1996, the percentage of ECS was 20%, while in 2006 it rose to 31% [12]. It is well known that ECS is associated with neonatal morbidity, persistent pulmonary hypertension, RDS, transient tachypnea of the newborn, and need for mechanical ventilation [15, 21-23]. Neonatal respiratory disorders at term pregnancies based on insufficient pulmonary gas exchange caused by unsatisfactory elimination of excess fluid from alveoli and a decrease of pulmonary blood perfusion [24].

Evidence which suggest that antenatal corticosteroids are effective in reducing RDS of neonates has already been known from Liggins and Howie [2] Antenatal corticosteroids which are mainly used for accelerating fetal lung maturation for women at risk of preterm birth or those who will undergo EECS are betamethasone and dexamethasone.

Glucocorticoids affect the development of various organs of the fetus. They increase the activity of ACTH in the adrenal glands resulting in the increase of the epinephrine concentration. These actions help the fetus to be prepared

Table 2. Complications related to antenatal corticosteroids administration and gestational week

Complications presentation					
	NO	**YES**	**OR**	**95%CI**	**P value**
37th gestation week					
corticosteroids administration					0.717
Yes	56 (96.6)	2 (3.4)	ref.		
No	60 (95.2)	3 (4.8)	1.40	0.23 – 8.69	
38th gestation week					
Corticosteroids administration 0.029					
Yes	149 (99.3)	1 (0.7)	ref.		
No	207 (95.4)	10 (4.6)	7.20	1.01 – 56.84	
39th gestation week					
Corticosteroids administration 0.645					
Yes	106 (99.1)	1 (0.9)	ref.		
No	121 (98.4)	.6)	1.75	0.16 – 19.60	
Total					
Corticosteroids administration 0.042					
Yes	311 (98.7)	4 (1.3)	ref.		
No	388 (36.4)	15 (3.7)	3.01	1.00 – 9.15	

Data are number of subjects and percentage (%); OR, odds ratio adjusted for mother's age and child's weight; CI, confidence interval.

for extrauterine life, as catecholamines affect the cardiovascular system of the fetus, glucose metabolism, and heat production [24].

Antenatal corticosteroids should not be avoided even if the delivery takes place earlier from the pass of 24 hours. It has been found that 15 hours after corticosteroids administration, a decrease of albumin in the lungs of the fetus, and of the intrapulmonary pressure, resulting in an increase of the overall volume and the elasticity of the lungs of the fetus, facilitates gas exchange and improves lung function of fetal [25].

Guidelines for antenatal corticosteroids administration were developed by the National Institutes of Health, the American, the Royal College of Obstetricians and Gynaecologists, and by the European Society of Perinatal Medicine [26-29]. The American College of Obstetricians and Gynecologists does not consider the indication of antenatal corticosteroids in reducing the risk of preterm birth after the 34th gestational week. Furthermore, according to the Royal College of Obstetricians and Gynaecologists, the decision to use corticosteroids after the 34th gestational week, was obtained according to the discretion of the obstetrician. Finally, the European Society of Perinatal Medicine supports the use of antenatal corticosteroids after the 34th week of gestation, when there are signs of immaturity of fetal lungs.

The steroids of choice to enhance lung maturation at risk of preterm birth are: 12 mg of betamethasone given intra-

muscularly in two doses, 24 hours prior or four doses of dexamethasone 6 mg given intramuscularly 12 hours prior. Specifically, the most extensively used dose to improve the lung function of newborns which will be born by an ECS, is the injection of 12 mg betamethasone 48 hours before the planned CS.

Concerning oral corticosteroids the data are insufficient regarding the absorption and availability. Corticosteroids administration into the amniotic fluid was associated with an increased likelihood of fetal death [30, 31].

A retrospective non-randomized study, showed that infants exposed prenatally to betamethasone injection, have a lower incidence of cystic periventricular leukomalacia than infants who received prenatal dexamethasone [32]. Another study showed that the risk of neonatal death is lower in the group that was administered antenatal betamethasone [33]. Because there are insufficient data on the long-term effects of prenatal dexamethasone injection, the use of both corticosteroid treatment are acceptable. A study which compared oral administration of dexamethasone with intramuscular administration, showed that oral administration showed a greater incidence of neonatal sepsis [34].

The Royal College of Obstetricians and Gynaecologists and the European Association of Perinatal Medicine, in their guidelines, suggest the administration of betamethasone while the American College of Obstetricians and Gynecologists does not adopt a preference between the two corticosteroids. Multiple courses of steroids are not routinely recommended because of a lack of consistent evidence showing additional benefit even in the case that a preterm labor occurs in a time of one week.

Trials of repeated doses of antenatal corticosteroids in animals concluded that there might be beneficial effects in terms of lung function, but also may lead to possible harmful effects, including growth and brain developmental delays [35]. A meta-analysis of five randomized trials, concluded that repeat doses of antenatal corticosteroids is more beneficial than single dose at the reduction and severity of neonatal lung disease of neonatal morbidity, but without any effect at the mortality [36]. Other studies, showed that repeated courses of antenatal corticosteroids are associated with a reduction in some measures of weight by being small for gestational age at birth children with a smaller head circumference [37]. The risks of repeated doses of antenatal corticosteroids to mothers are hyperglycemia, infections, and suppression of the hypothalamic -pituitary-adrenal glands.

The National Institutes of Health does not recommend the general use of repeated doses of antenatal corticosteroids, due to insufficient clinical data [26]. The European Society of Perinatal Medicine does not recommend the repeated use of corticosteroids, however, if the clinician decides a repeat dose, then a single dose of betamethasone should be given [38]. The number of repeated doses should be less than four, the parents must be informed about the lack of evidence of long-term results in neonates, and repeated courses of corticosteroids should not be used routinely. Repeated doses should be reserved for women enrolled in randomized controlled trials where the children must have a longer follow-up concerning their physical and neurological development.

The Royal College of Obstetricians and Gynaecologists (2010) suggests that corticosteroids should only be considered with caution in those pregnancies where the first course was given at less than 26 weeks of gestation and another obstetric indication arises later in pregnancy [28]. On the other hand, the American College of Obstetricians and Gynecologists (2008) does not recommend the repeated doses [27].

Concerns have been raised about the possible long-term effects of treatment with antenatal corticosteroids prior to delivery by ECS. According to a Cochrane meta-analysis [39] and the guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG 2004) [40], a single dose of antenatal corticosteroids is not observed to cause an adverse effect on physical, neurological, and cognitive development of infants [41, 42].

The guidelines of the Royal College of Obstetricians and Gynaecologists discusses the safety of antenatal corticosteroids, but seems to be associated with short-term adverse effects to mother or fetus, while there are no long-term adverse neurological or cognitive effects. In premature infants, antenatal corticosteroids injection has been associated with changes in blood pressure and with increased insulin response to glucose in the early years of adulthood [43]. Therefore, studies in humans have shown that increasing the number of doses of glucocorticoids, in order to enhance the maturation of the lungs is associated with decreased birth weight and behavioral disorders in the age of three [44].

Antenatal corticosteroids administration appears to affect the fetal biophysical profile. The fetal heart rate is increased, the variability is reduced, and the number of accelerations decreases at the first and the second day after administration and returns to normal on the third day. This effect on the cardiac function of the fetus, which can mimic fetal distress, should be known to all clinicians in order to avoid an undue iatrogenic induction of labor [45]. Other parameters of the biophysical profile of the fetus that may be affected by antenatal corticosteroids administration is the reduction of fetal movements and breathing.

Infants who received antenatal corticosteroids, showed an increase in the number of neutrophils, but without any effect on their functionality and a reduction in the number of lymphocytes without associated with an adverse effect on the health of newborns [46].

According to Royal College of Obstetricians and Gynaecologists, specialist should be exercised when giving corticosteroid therapy to women with systemic infection

including tuberculosis or sepsis. The use of corticosteroids may has as risk, the activate latent infections or exacerbate fungal infections. For the Royal College of Obstetricians and Gynaecologists there is no contraindication for antenatal corticosteroids administration to pregnant women with premature rupture of fetal membranes which have an increased risk for chorioamnionitis. Additionally, American College of Obstetricians and Gynecologists (2008) [27] suggests the use of corticosteroids if there is an indication of coexisting fetal lung immaturity and the European Society of Perinatal Medicine does not recommend the use of corticosteroids after 32 weeks of gestation, in pregnant women with premature rupture of membranes, whereas after 32 weeks, the risks of chorioamnionitis is greater than the risks of prematurity [27-29].

Antenatal corticosteroids present the same indication for administration in multiple pregnancies and also, showing benefit in reducing neonatal mortality and morbidity. In a retrospective study by Quist-Therson *et al.* [47], found that antenatal steroid therapy did not reduce the incidence of RDS in multiple gestation white infants. According the efficacy of the antenatal corticosteroids in non multiple pregnancies corticosteroids are given even in multiple pregnancies [47].

Women with insulin-dependent diabetes or gestational diabetes had not a contraindication to antenatal corticosteroid treatment for fetal lung maturation. It is noteworthy that attention should be given at the proper regulation of blood sugar levels because of the transient induced hyperglycemia and possible glucose intolerance [48]. In mothers, there is also a transient increase in white blood cells 24 hours after administration of corticosteroids [49].

Pregnancies from 24 up to 35^{+6} weeks of pregnancy which characterized by intrauterine growth retardation are also included in the group of pregnancies of the Royal College of Obstetricians and Gynaecologists which recommends antenatal corticosteroids administration.

Generally, in this study the single-dose of antenatal betamethasone before performing an ECS, has a beneficial effect on newborns by improving their lung function. There are some limitations to this study. This is a randomized study and therefore presents potential biases of observational studies. To reduce these biases, were enrolled only women who gave birth at the University Hospital of Alexandroupolis. The small number of women in which ECS was performed is another weak point of this study.

Conclusion

In conclusion, treatment with antenatal corticosteroids prior to delivery by ESC has been shown to outweigh the improvement in lung function of newborns, compared to the group of women which did not receive betamethasone administration, especially in the group of women who were in the 38th gestational week. Improvement in lung function of neonates is observed (even in a lower incidence) in the total of women who received antenatal corticosteroids (regardless to gestational age in which they were), against women which did not have corticosteroid administration.

References

[1] Schaap A.H., Wolf H., Bruinse H.W., Smolders-De Haas H., Van Ertbruggen I., Treffers P.E.: "Effects of antenatal corticosteroid administration on mortality and long-term morbidity in early preterm, growth-restricted infants". *Obstet. Gynecol.*, 2001, *97*, 954.

[2] Liggins G.C., Howie R.N.: "A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants". *Pediatrics*, 1972, *50*, 515.

[3] Crowley P., Chalmers I., Keirse M.J.: "The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials". *Br. J. Obstet. Gynecol.*, 1990, *97*, 11.

[4] Stutchfield P., Whitaker R., Russell I., Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team: "Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial". *BMJ*, 2005, *331*, 662.

[5] Crowley P.: "Prophylactic corticosteroids for preterm birth". Cochrane Database Syst Rev., 2000, *2*, CD000065. Review. Update in: *Cochrane Database Syst. Rev.*, 2006, *3*, CD000065

[6] Bauer C.R., Morrison J.C., Poole W.K., Korones S.B., Boehm J.J., Rigatto H., Zachman R.D.: "A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy". *Pediatrics*, 1984, *73*, 682.

[7] Smith L.M., Ervin M.G., Wada N., Ikegami M., Polk D.H., Jobe A.H.: "Antenatal glucocorticoids alter postnatal preterm lamb renal and cardiovascular responses to intravascular volume expansion". *Pediatr. Res.*, 2000, *47*, 622.

[8] Costalos C., Gounaris A., Sevastiadou S., Hatzistamatiou Z., Theodoraki M., Alexiou E.N., Constandellou E.: "The effect of antenatal corticosteroids on gut peptides of preterm infants—a matched group comparison: corticosteroids and gut development". *Early Hum. Dev.*, 2003, *74*, 83.

[9] Ford W.D., Kirby C.P., Wilkinson C.S., Furness M.E., Slater A.J.: "Antenatal betamethasone and favourable outcomes in fetuses with 'poor prognosis' diaphragmatic hernia". *Pediatr. Surg. Int.*, 2002, *18*, 244

[10] Ramachandrappa A., Jain L.: "Elective cesarean section: its impact on neonatal respiratory outcome". *Clin. Perinatol.*, 2008, *35*, 373.

[11] Grover T.R., Ackerman K.G., Le Cras T.D., Jobe A.H., Abman S.H.: "Repetitive prenatal glucocorticoids increase lung endothelial nitric oxide synthase expression in ovine fetuses delivered at term". *Pediatr. Res.*, 2000, *48*, 75.

[12] Martin J.A., Hamilton B.E., Sutton P.D., Ventura S.J., Mathews T.J., Osterman M.J.: "Births: final data for 2008". *Natl. Vital Stat. Rep.*, 2010, *59*, 3.

[13] Madar J., Richmond S., Hey E.: "Surfactant-deficient respiratory distress after elective delivery at 'term' ". *Acta. Paediatr.*, 1999, *88*, 1244.

[14] Gerten K.A., Coonrod D.V., Bay R.C., Chambliss L.R.: "Cesarean delivery and respiratory distress syndrome: does labor make a difference?" *Am. J. Obstet. Gynecol.*, 2005, *193*, 1061.

[15] Hansen A.K, Wisborg K., Uldbjerg N., Henriksen T.B.: "Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study". *BMJ*, 2008, *336*, 85.

[16] Brown M.J., Olver R.E., Ramsden C.A., Strang L.B., Walters D.V.: "Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb". *J. Physiol.*, 1983, *344*, 137.

[17] Harding J.E., Pang J., Knight D.B., Liggins G.C.: "Do antenatal corticosteroids help in the setting of preterm rupture of membranes?" *Am. J. Obstet. Gynecol.*, 2001, *184*, 131.

[18] Menacker F., Declercq E., Macdorman M.F.: "Cesarean delivery: background, trends, and epidemiology". *Semin. Perinatol.*, 2006, *30*, 235.
[19] NHS Information Centre: "Method of delivery". *In: Office for National Statistics*, 2009. The National Statistics Publication Hub.
[20] Wales Assembly Government: "Maternity statistics-method of delivery in Wales". *In:* Office for National Statistics, 2009. Annual Report and Resource Accounts 2008/09, vol. 1.
[21] Villar J., Carroli G., Zavaleta N., Donner A., Wojdyla D., Faundes A., *et al.*: "Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study". *BMJ*, 2007, *335*, 1025.
[22] Hansen A.K., Wisborg K., Uldbjerg N., Henriksen T.B.: "Elective caesarean section and respiratory morbidity in the term and near-term neonate". *Acta Obstet. Gynecol. Scand.*, 2007, *86*, 389.
[23] Tita A.T., Landon M.B., Spong C.Y., Lai Y., Leveno K.J., Varner M.W., *et al.*: "Timing of elective repeat cesarean delivery at term and neonatal outcomes". *N. Engl. J. Med.*, 2009, *360*, 111.
[24] Paganelli S., Soncini E., Gargano G., Capodanno F., Vezzani C., La Sala G.B.: "Retrospective analysis on the efficacy of corticosteroid prophylaxis prior to elective caesarean section to reduce neonatal respiratory complications at term of pregnancy: review of literature". *Arch. Gynecol. Obstet.*, 2013, *288*, 1223.
[25] Ikegami M., Polk D., Jobe A.: "Minimum interval from fetal detamethasone treatment to postnatal lung responses in preterm lambs". *Am. J. Obstet. Gynecol.*, 1996, *174*, 1408.
[26] NIH Consensus Development Panel: "Antenatal corticosteroids revisited: repeat courses-National Institute of Health Consensus Development Conference statement, August 17-18, 2000". *Obstet. Gynecol.*, 2001, *98*, 144.
[27] Committee on Obstetric Practice: "ACOG committee opinion: antenatal corticosteroid therapy for fetal maturation". *Obstet. Gynecol.*, 2008, *111*, 805.
[28] Royal College of Obstetricians and Gynaecologists (RCOG): "Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality. "Green-top Guideline No. 7 October 2010". Available at: https://www.glowm.com/pdf/Antenatal%20Corticosteroids%20to%20Reduce%20Neonatal%20Morbidity.pdf
[29] Miracle X., Di Renzo G.C., Stark A., Fanaroff A., Carbonell - Estrany X., Saling E., Coordinators of WAPM Prematurity working group.: "Guideline for the use of antenatal corticosteroids for fetal maturation". *J. Perinat. Med.*, 2008, *36*, 191.
[30] Gilbert W.M., Eby - Wilkens E., Plopper C., Whitsett J.A., Tarantal A.F.: "Fetal monkey surfactants after intra - amniotic or maternal administration of betamethasone and thyroid hormone". *Obstet. Gynecol.*, 2001, *98*, 466.
[31] Moss T.J.M., Mulrooney N.P., Nitsos I., Ikegami M., Jobe A.H., Newnham J.P.: "Intra - amniotic corticosteroids for preterm lung maturation in sheep". *Am. J. Obstet. Gynecol.*, 2003, *189*, 1389.
[32] Baud O., Foix-L'Helias L., Kaminski M., Audibert F., Jarreau P.H., Papiernik E., *et al.*: "Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants". *N. Engl. J. Med.*, 1999, *341*, 1190.
[33] Lee B.H., Stoll B.J., McDonald S.A., Higgins R.D., National Institute of Child Health and Human Development Neonatal Research Network: "Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone". *Obstet. Gynecol. Surv.*, 2006, *61*, 568.
[34] Egerman R.S., Mercer B.M., Doss J.L., Sibai B.M.: "A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome". *Am. J. Obstet. Gynecol.*, 1998, *179*, 1120.
[35] Aghajafari F., Murphy K., Matthews S.: "Repeated doses of antenatal corticosteroids in animals: A systematic review". *Am. J. Obstet. Gynecol.*, 2002, *186*, 843.
[36] Crowther C.A., Harding J.E.: "Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease". *Cochrane Database Syst. Rev.*, 2007, *3*, CD003935.
[37] Thorp J.A., Jones P.G., Knox E., Clark R,H.: "Doses antenatal corticosteroid therapy affect birth weight and head circumference". *Obstet. Gynecol.*, 2002, *99*, 101.
[38] Miracle X., Di Renzo G.C., Stark A., Fanaroff A., Carbonell-Estrany X., Saling E., *et al.*: "Recommendations and guidelines for perinatal practice. Guideline for the use of antenatal corticosteroids for fetal maturation". *J. Perinat. Med.*, 2008, *36*, 191.
[39] Roberts D., Dalziel S.: "Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth". *Cochrane Database Syst. Rev.*, 2006, *3*, CD004454.
[40] Royal College of Obstetricians & Gynaecologists: "Antenatal corticosteroids to prevent respiratory distress syndrome Greentop guideline". London: Royal College of Obstetricians and Gynaecologists. RCOG Green Top Guideline N. 7, October 2010.
[41] Walfisch A., Hallak M., Mazor M.: "Multiple courses of antenatal steroids: risks and benefits". *Obstet. Gynecol.*, 2001, *98*, 491.
[42] Yeh T.F., Lin Y.J., Lin H.C., Huang C.C., Hsieh W.S., Lin C.H., Tsai C.H.: "Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity". *N. Engl. J. Med.*, 2004, *350*, 1304.
[43] Doyle L.W., Ford G.W., Davis N.M., Callanan C.: "Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children". *Clin. Sci. (Lond.)*, 2000, *98*, 137.
[44] Newnham J.P.: "Is prenatal glucocorticoid administration another origin of adult disease?" *Clin. Exp. Pharmacol. Physiol.*, 2001, *28*, 957.
[45] Mulder E.J., Derks J.B., Visser G.H.: "Antenatal corticosteroid therapy and fetal behavior: a randomized study of the effects of betamethasone and dexamethasone". *Br. J. Obstet. Gynecol.*, 1997, *104*, 1239.
[46] Barak M., Cohen A., Hershkowitz S.: "Total leukocyte and neutrophil count changes associated with antenatal betamethasone administration in preterm infants". *Acta Paediatr.*, 1992, *81*, 760.
[47] Quist - Therson E.C., Myhr T.L., Ohlsson A.: "Antenatal steroids to prevent respiratory distress syndrome: multiple gestation as an effect modifier". *Acta. Obstet. Gynecol. Scand.*, 1999, *78*, 388.
[48] National Institute for Health and Clinical Excellence: "NICE Clinical Guideline 63: Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period". London: NICE, 2008. Available at: ww.nice.org.uk/nicemedia/pdf/CG063PublicInfo.pdf
[49] Diebel N.D., Parsons M.T., Spellacy W.N.: "The effects of betamethasone on white blood cells during pregnancy with pPROM". *J. Perinat. Med.*, 1998, *26*, 204.

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