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CORTICOPROFILAXIA WITH GLUCOCORTICOIDS IN FETUSES OVER 36 WEEKS. RESPIRATORY ADAPTATION AND NEUROLOGICAL DIAGNOSIS OF THE NEWBORN
SUMMARY OF THE DOCTORAL THESIS

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In the human body, glucocorticoids are steroid stress hormones with important effects on the immune system. They are synthesized in the cortical area of the adrenal gland (cortisone and hydrocortisone) and have numerous roles and effects on devices and systems. The important anti-inflammatory effects of natural glucocorticoids can be achieved by administration of synthetic glucocorticoid (GC) analogues such as prednisone, prednisolone, dexamethasone, betamethasone.

Synthetic glucocorticoids have been used in human medicine for over 70 years, having been discovered in the late 1950s as a treatment for rheumatoid arthritis, but the effects on the body are not fully understood. All synthetic GCs are structurally similar to cortisol and corticosterone, which are the major endogenous GCs in mammals.

The use of GCs is carried out in both clinical and preclinical studies, their importance lies in their anti-inflammatory effects and immunosuppressive actions. By easily attaching to the glucocorticoid receptor at the cellular level, synthetic GCs influence the hypothalamic-pituitary axis, and interfere with cortisol levels.

There is a wide range of recommendations regarding the administration of synthetic GCs based on their strong anti-inflammatory and immunosuppressive effects.

Historically, GCs have been used during pregnancy with the aim of foetal lung maturation since the mid-1950s, when the scientist Liggins G. observed a better respiratory adaptation of lambs born prematurely if they were administered to pregnant ewes before parturition.

Since 1994, the recommendation for the use of synthetic GCs (Betamethasone or Dexamethasone) has been introduced worldwide for all pregnancies at risk of premature birth with a gestational age of less than 32 weeks, with the aim of improving the postnatal adaptation of the new-born, reducing morbidity and neonatal mortality.

The beneficial effects on the foetal lung through their antenatal administration consist in stimulating the synthesis of surfactant at the level of type II pneumocytes, which ensures better pulmonary compliance and a reduction of the surface tension at the level of the alveolus, thus improving gas exchange. Also, another important effect at the cellular level consists in increasing the transcription and synthesis of epithelial Na+ channels from the lung level and aquaporins, with implications in the resorption process of foetal lung fluid.

The risk categories in the development of respiratory distress syndrome are predominately represented by premature new-borns with VG under 34 weeks, which is why there is a firm

recommendation included in all obstetrics and gynaecology protocols worldwide, for the antenatal administration of GC in pregnancies with risk of premature birth.

Clinical data from the last 20 years have correlated premature new-borns with VG over 34 and those early term with the risk of difficult postnatal adaptation, through the appearance of respiratory distress, transient neonatal tachypnoea, with the need for admission to neonatal intensive care units (NICU) and ensuring respiratory support (oxygen under the cephalic tent, CPAP, mechanical ventilation). Following these findings, in most states, a single course of corticosteroids is recommended for this gestational age category as well.

By extrapolating the information obtained in the last decade about the benefits of antenatal administration of corticosteroids, in conjunction with the information about the increase in the rate of caesarean births, it was possible to expand the use of this therapy also in the case of early term new-borns.

The benefits of antenatal corticoprophylaxis on the foetus and the new-born in its adaptation to extrauterine life, by reducing the risk of respiratory events, such as respiratory distress, neonatal respiratory tachypnoea, are indisputable. But the researchers' concerns are about insufficient data on side effects, both short-term and long-term. GC easily crosses the placenta and reaches high concentrations in the foetal blood, shortly after administration, the serum concentration decreases due to the rapid installation of the mineralocorticoid effect and by influencing the endogenous secretion of GC, through the hypothalamic-pituitary axis.

As a short-term consequence, lower serum glucose levels have been observed among neonates born to mothers who received antenatal corticosteroid prophylaxis, especially in those who received the treatment near the time of birth, probably through -a mechanism of foetal hyperinsulinism, in response to GC-induced maternal hyperglycaemia.

Since the influences of synthetic glucocorticoids on the hypothalamic-pituitary axis are not fully known, several studies have been carried out over time, which aimed to follow the neurocognitive development of the categories of new-borns who benefited from antenatal GC administration. The results of these studies performed mainly on premature new-borns who were administered several corticoprophylaxis courses, emphasized the appearance of personality development disorders, lack of stress tolerance and delays in acquisition skills at school age.

It should be noted that there are currently few studies in the literature regarding the administration of antenatal GCs to VGs beyond 36 weeks, probably starting from the premise that

the immediate postnatal adaptation of these new-borns is generally favourable and surfactant secretion is sufficient to ensure the success of the transition to extrauterine life. However, the increasing rate of caesarean births at 36 weeks 6/7 – 37 weeks 6/7 days, often in the absence of labour, have generated changes in the adaptation of girls to extrauterine life, manifested by respiratory distress, tachypnoea transient neonatal, HTPP with the need for intensive neonatal therapeutic support.

Currently, the global prevalence of caesarean births has increased considerably, so the WHO (World Health Organization) warned that in 2021, 1 in 5 children was born this way, reaching a percentage of 21% of all births to be represented by caesarean births. In Romania, at present, there are no definite statistical data indicating the percentage of caesarean births, but the trend of caesarean births is constantly increasing, far exceeding the percentages of the countries of north western Europe or the states of North America. From the latest statistical data, our country is worryingly close to countries such as those in the Caribbean, Egypt, the Balkans or East Asia.

Regarding the current state of knowledge, I mention studies that evaluated the adaptation of the new-born to extrauterine life following caesarean delivery, at a gestational age of more than 36 weeks (studies that I will detail during this research thesis). Thus, statistically significant data were described regarding the occurrence of respiratory events in new-borns extracted by caesarean section, at ages over 36 weeks of gestation, especially in the absence of induction of labour, as well as the effects of antenatal corticoprophylaxis on these categories of new-borns .

Also, during the research thesis, studies evaluating the adverse effects of the administration of antenatal corticosteroid prophylaxis will be detailed, taking into account the influence of synthetic corticosteroids on the hypothalamic-pituitary axis.

Our study belongs to the observational prospective studies, which present the differences obtained between two groups of new-borns (control group without antenatal dexamethasone administration and the study group of new-borns with antenatal dexamethasone administration). The study was carried out over a period of 3 years (2017-2019) and includes a number of 81 new-borns from dispensary pregnancies, with a gestational age between 36 weeks and 38 + 6/7 weeks, extracted by caesarean section, with an antenatal course of dexamethasone. The control group included a number of new-borns of the same gestational age as those in the study group, extracted by caesarean section and who did not receive antenatal dexamethasone.

After analysing the data regarding the presence of the functional respiratory syndrome for which the new-borns required admission to the Neonatal Intensive Care Unit and the specific care in the group of new-borns who did not receive antenatal dexamethasone and who were extracted by caesarean section, this association was burdened by statistical significance.

At the same time, after analysing the association of the risk of hypoglycaemia in the group of new-borns from pregnancies where dexamethasone was administered before birth, a tendency towards lower blood glucose values (< 40 mg/dL) was observed in the first hour of life.

On the other hand, after analysing the neurocognitive behaviour after discharge from the maternity hospital, no significant differences were revealed between the two groups of new-borns.

The peculiarity of the study consisted in:

1. Increased rate of caesarean births compared to vaginal births

2. The majority of patients who opted for caesarean delivery are women with higher education aged between 28-35 years

The limits of the study were primarily represented by the unicentric character, it being carried out exclusively in the Obstetrics-Gynaecology and Neonatology Clinic of the "Elias" University Emergency Hospital.

Secondly, the follow-up of the new-borns who benefited from antenatal corticoprophylaxis could be carried out mainly in the first month of life, after that maintaining the connection with the patients became difficult, the vast majority going to the offices of family doctors or paediatricians. The importance of following up these children from the point of view of neurodevelopment is at older ages, i.e. at school age, where the multidisciplinary collaboration of a family doctor or paediatrician and a paediatric neurologist is recommended.

Specifying the limitations of the research thesis, I want to open the way to new ideas and study opportunities, by forming teams that follow the evolution of new-born patients at different developmental ages, thus being able to carry out a more faithful and consistent research.

Notions of embryology

The development of the respiratory system is carried out by a complex of embryological processes, which involve multiple embryonic structures, most of them starting from the ectoderm,

and which originate from the first weeks of gestation. Later, in intrauterine life, the closeness to the end of this process can be observed by the appearance of foetal respiratory movements. (1)

The respiratory bud appears around the 4th week of gestation in the form of a diverticulum originating from the ventral wall of the proenteron (primitive intestine). Both respiratory bud formation and intrauterine growth and differentiation are mediated by the transcription factor TBX4, synthesized in the endoderm cells of the intestinal tube in the area of origin of the respiratory diverticulum. Thus, the lung epithelium is endodermal in origin, and the cartilaginous, muscular, and connective components are derived from the splanchnic mesoderm surrounding the proenetron. (1,2)

In evolution, from the fifth week of gestation, the diverticulum expands caudally, leading to the formation of the two tracheoesophageal ridges, which separate it from the foregut. Through the fusion of the two ridges and the formation of the tracheoesophageal septum, the detachment of the diverticulum and the appearance of bronchial buds and the formation of the trachea occur.

The appearance and growth of the right and left main bronchi, with subsequent differentiation into 3 right secondary bronchi and 2 left secondary bronchi, begins in the fifth week of gestation, representing the beginning of the formation of the lung lobes. The growth in the caudal and respectively lateral directions of the pulmonary primordia, with the penetration into the pleuroperitoneal channels, thus determines the occupation of an increasing volume of the embryonic body and the formation of the pleural cavities by the elongation of the pleuroperitoneal channels, the displacement of the transverse septum and the stomach. The two sheets of pleural serosa (visceral and parietal) will develop from the mesothelium of the pleuroperitoneal channels. (2,3)

In evolution, embryonic lung development takes place during 4 stages, starting with the pseudo glandular phase from week 5-6 of gestation, which involves the branching process of the main bronchi until the formation of terminal bronchioles.

In the second phase, the canalicular phase, breathing becomes possible through the appearance of the alveolar ducts, a stage that takes place between weeks 16-26 of gestation. From week 26 until birth, the terminal sacs appear and during all this time the foundations for the formation of the alveolo-capillary membrane are laid (phase of the terminal sacs).

The number of terminal sacs gradually increases during the last 2 months of intrauterine life, and this process extends into the first years after birth.

The last phase, the alveolar phase, begins at the age of 8 months of life and involves the formation of new alveoli, a process that continues continuously during the paediatric period until close to the age of 10 years. (1–3)

Notions about surfactant

It is well known that the role of surfactant consists in reducing the surface tension at the alveolar level, thus preventing the collapse of the alveoli at the end of exhalation and reducing respiratory effort. (4)

Surfactant (derived from the English acronym SURFace ACTive AgeNT) is essential to ensure survival. In its biochemical structure, phospholipid substances were described in a predominant percentage, in the mixture, especially dipalmitate phosphatidyl choline, but also four proteins, SP-A, SP-B, SP-C, SP-D, with an essential role in ensuring the quality of the surfactant and integration of immunological functions. (5,6)

The hydrophobic proteins SP-B and SP-C together with phosphatidyl choline have the property of reducing surface tension so that alveolar inflation requires less inspiratory pressure. As a result, they contribute to alveolar stability and decrease the risk of atelectasis. (4,7,8)

Hydrophilic proteins, SP-A and SP-D participate in the performance of the immune response, as a result they are able to bind to bacterial, viral or fungal antigens, forming protein complexes that activate cells of the immune system and thus trigger a series of defense reactions. (7,8)

Immunosuppressive actions of certain surfactant-associated phospholipids such as phosphatidylglycerol are also known. In contrast, preclinical experiments have demonstrated the effect of microbial pathogens on surfactant synthesis and secretion, through the degradation of surfactant-associated proteins by bacterial proteinases.

Alteration of core components of the surfactant structure has been classically described in surfactant deficiency neonatal respiratory distress syndrome (SDR). Surfactant replacement therapy with exogenous surfactant is still the mainstay in the treatment of this pathology characteristic of the premature new-born. Respiratory distress syndrome due to surfactant deficiency is the main cause of respiratory function disturbance in new-borns, but in recent years,

other acute or chronic lung pathologies have been described that interfere and cause compositional deficiencies, both quantitatively and qualitatively of the surfactant.

Under certain circumstances, surfactant can accumulate in excess in the alveoli causing an increase in surfactant. These disorders are described in the pathology called alveolar proteinosis (pulmonary alveolar lipoproteinosis), which is a disorder characterized by a functional deficiency of the granulocyte-macrophage colony-stimulating receptor or the development of antibodies to the granulocyte-macrophage colony-stimulating factor (lack of growth factor). (5)

Indeed, these seminal observations helped propel surfactant replacement therapy as an approach that revolutionized the treatment of RDS in preterm infants. However, in the 1990s, scientists discovered some additional important biological properties of this substance, in terms of providing host immunity against microbial infections and immunomodulatory activity. (3,4

Notions of foetal respiratory movements and adaptation to extrauterine life

The notions of foetal respiratory movements (FBM/MRF) were initially described, following studies carried out on animal faces (sheep) and following which it was found that FBM initially trains the movements of the diaphragm, thus lowering the intrathoracic pressure by about 3-4 mmHg . However, each foetal movement produces insignificant changes in lung volumes (< 1 ml), due to three factors: amniotic fluid viscosity which is increased compared to air, short inspiratory time, and increased upper airway resistance. (8,15,16)

The importance of these foetal respiratory movements is well established by their involvement in the mechanisms of increasing pulmonary compliance, thus, the presence of episodes of apnea causes a decrease in the elimination of lung liquid through the narrowing of the larynx. When periods of foetal respiratory movements intensify, they stimulate the opening of the larynx and the elimination of lung fluid. (8,17)

Insights into lung epithelial Na+ channels

The alveolar epithelium is composed of two distinct types of alveolar cells, alveolar cells or type I pneumocytes (AT1) and type II pneumocytes (AT 2). (19)

The clearance of lung fluid is essential in the process of adapting the new-born to extrauterine life. Epithelial Na+ channels (ENaC) and the Na+/K+-ATPase pump, induced by the enzyme serum-glucocorticoid-inducible kinase (SGK1) and also aquaporins are important links in

the transition from the foetal pulmonary secretory phase to the absorptive phase pulmonary, after birth. (20,21)

Birth stress by releasing a large amount of catecholamines (norepinephrine) into the foetal blood, facilitates postnatal pulmonary adaptation, mainly by modulating Na^+ epithelial channels at the lung level. (22)

The association between expression of ENa^+C, the Na+/K+-ATPase pump, SGK1, and cord blood norepinephrine concentration reveals the importance of labour and delivery stress in stimulating lung fluid clearance. The contribution of these structures in the process of adaptation of the new-born to immediate extrauterine life is indisputable. (20,22,23)

Na^+ is transported from the apical surface of AT1 and AT2 cells via ENa^+C channels. Electroneutrality is preserved by the movement of the Cl- ion through CFTR or CLC channels at the level of AT2 cells. Na+ is transported across the basement membrane of alveolar cells into the interstitium via the Na+/K+-ATPase pump. Cyclic nucleotide (CNGL) channels are an alternative for intracellular Na+ and Ca2+ transport. (22,24)

Disturbance of lung fluid clearance can cause the appearance of a specific neonatal pathology, transient neonatal tachypnoea, the most common cause of respiratory distress in the first hours of life in full-term or early-term new-borns. Neonatal transient tachypnoea (TTN) affects 2.5% of full-term new-borns and 20% of early-term new-borns extracted by caesarean section, representing a pathology that belongs exclusively to this category of new-borns. (20.23)

The switch from the pulmonary secretory phase to the absorptive phase that begins near birth and continues throughout labour, continuing into the first hours after birth, has been associated with the release of a surge of glucocorticoids and catecholamines. During birth, thus reaching the maximum level of the concentration of catecholamines involved in this process. (20)

Studies carried out in recent years have concluded that the level of catecholamines is lower in the case of new-borns extracted by caesarean section, compared to the group of new-borns that come from physiological, vaginal births. (23,24)

Recent research carried out on animal groups, in vitro, with the aim of explaining as well as possible the connection between the presence of increased concentrations of glucocorticoids and catecholamines and the activation of the enzyme serum glucocorticoid-inducible kinase (SGK1), demonstrated that the presence of increased levels of SGK1 has been associated with increased expression and activation of pulmonary epithelial sodium channels. (23,24)

However, molecular studies in human models cannot yet be performed, so the mechanism of lung fluid absorption remains incompletely elucidated. The molecular distribution at the level of lung epithelial cells in the first hours of life has an important role in the respiratory adaptation of the new-born and remains in the attention of scientists. (20.23)

Notions about caesarean section

Birth by caesarean section is an increasingly common surgical procedure worldwide, many of these interventions being performed in the absence of a medical indication, practically at the request of the patient. If at the beginning of the 1990s the rate of births by this method was 7% worldwide, according to the WHO (World Health Organization), this percentage has tripled, and the trend tends to be in a constant increase, so that it is estimated to reach a percentage of approximately 29% until the year 2030.(25)

As far as Romania is concerned, there are no exact statistical data related to the prevalence of caesarean births. In our Clinic in the Elias University Emergency Hospital, we performed an observational retrospective statistical analysis over five years (2017, 2018, 2019, 2020, 2021), following the evolution of the method of delivery. Thus, during the five years studied, the trend is also upward in our clinic, to the detriment of physiological births, most patients being patients from the category of primiparous women with a gestational age of up to 41 weeks without associated pathologies and pregnant women who have already had a such intervention in the antecedents. (31)

Notions about antenatal corticosteroid therapy

Administration of corticosteroids in pregnancies at risk of preterm birth is one of the most important antenatal therapies available for such situations, which aims to improve neonatal prognosis by significantly reducing neonatal morbidity and mortality. The beneficial effects on the subsequent evolution of new-borns are demonstrated by the significant reduction in the severity and frequency of respiratory distress syndrome, intracranial haemorrhage, ulcerative necrotizing enterocolitis and mortality in the case of these children from mothers who were administered

corticosteroids antenatal, compared to new-borns from pregnancies where corticoprophylaxis could not be performed.

The corticosteroids recommended by obstetrics-gynaecology societies at the international level, for the purpose of prophylaxis for foetal lung maturation in pregnant women at risk of premature birth, are dexamethasone and betamethasone. The doses and the way of administration are almost identical, both are administered at least 48 hours before the birth, and the effects in the case of betamethasone were observed as early as the first 6 hours after the administration of the first dose. (34,35,38)

The protocol for the administration of corticosteroid prophylaxis in pregnant women at risk is the same in most states and involves, depending on the availability of medication in the respective countries and the protocols of each individual clinic, prophylaxis with either dexamethasone with the administration of 4 doses (6 mg) intramuscularly at an interval of 12 hours, or the one with betamethasone 2 doses (12 mg) at an interval of 24 hours. The maximum serum concentration in the maternal blood after the administration of betamethasone is established one hour after the injection, and the half-life in the foetal blood is 12 hours, so that 48 hours after the last administration no traces of betamethasone can be identified in the maternal or foetal blood. Administration of dexamethasone in lower doses (6 mg) over a longer period of time, 48 hours, allows maintaining serum concentrations over a longer period of time and prevents the rapid ascent of concentrations. Reaching the maximum beneficial potential of the treatment is 2-7 days after the first administered dose. Both betamethasone and dexamethasone cross the placenta and are largely not inactivated by placental enzymes. (33,35,39,41)

Corticosteroids stimulate the secretion of surfactant from the foetal lung, regulate the development of the lung, brain, and other organs, and activate the enzyme system in the gut. One of the topics most often discussed at the international level is that related to the administration of betamethasone, in favour of dexamethasone, considering that the adverse effects, especially those related to the delay in acquisitions at school age in this category of new-borns, are less .

Notes about the complications of antenatal corticotherapy

1. Early complications

An incidental and unanticipated finding was the presence of a large number of neonates who developed hypoglycemia (blood glucose < 40mg/dL) among neonates who received antenatal

corticosteroid prophylaxis (24% versus 15%; relative risk 1.60) compared to the control group. In the group of hypoglycemic neonates, the number of blood glucose measurements, nadir levels, maternal blood glucose values, or treatment required to correct hypoglycemia were not discussed, and discharge of these children was found to be on average 2 days later than among those without hypoglycemia, suggesting that this event was self-limited.(56)

The information available so far in the specialized literature supports that a single course of corticosteroids administered antenatally does not produce adverse effects in the neonatal period, respectively the immunosuppressive effect of glucocorticoids does not seem to increase the risk of infection in the new-born. However, there are also studies in developing countries that have investigated antenatal glucocorticoid administration and the incidence of neonatal infections and have reported an increase in neonatal mortality in neonates exposed to antenatal steroid therapy. The increased risk of neonatal mortality was associated with severe neonatal infection, specifically in low-birth-weight infants. Maternal infection has been associated with neonatal infection. Thus, it has been suggested that the presence of infection in the new-born and in the mother could be an adverse effect of corticoprophylaxis, through the immunosuppressive effect produced by glucocorticoids, but there are not enough data to confirm this perspective and further studies are needed to elucidate this theory. (43,46,48)

Studies without the short-term effects of glucocorticoids have reported reduced basal and stress cortisone secretion in neonates exposed to corticosteroid prophylaxis and a greater number of low-for-gestational-age (SGA) term neonates . Repeated courses of corticosteroids in female mice also resulted in reduced placental size and associated intrauterine growth restriction in pups. However, more studies are needed to clarify the controversies regarding the association between the administration of corticoprophylaxis and low birth weight for gestational age or even foetal growth restriction.

2. Late complications

The short-term effects of antenatal corticosteroids on improving postnatal prognosis by reducing neonatal mortality and morbidity are well known, long-term effects on development in pediatric and even adult age remain uncertain and are under investigation.

Concerns about the late effects of antenatal corticosteroids on neurodevelopment are justified, as corticosteroids cross the placenta and readily enter the foetal circulation, then cross the blood-brain barrier, and as a result may affect foetal brain development.

With the development of protocols that established the exact number of corticosteroid courses that can be used in pregnancy according to gestational age, their excessive use was limited and thus the risk of harm to the new-born was reduced. On the other hand, the number of new-borns who received dexamethasone or betamethasone increased by the administration recommendations and at gestational ages over 34 weeks.

Current studies discuss the link between the number of courses administered in pregnancy and the likelihood of neurodevelopmental disruption at school age, such that new-borns exposed to more than two courses in utero are at greater risk of developing cognitive or behavioural disorders. (58)

As is well known, prenatal administration of synthetic glucocorticoids (GCs) accelerates foetal lung maturation and significantly decreases neonatal mortality and morbidity in preterm neonates with a gestational age of less than 34 weeks. But exposure to elevated levels of glucocorticoids influences the normal developmental trajectory, and in this sense influencing foetal HPA development is discussed. Evidence from experimental animal work suggests that this exposure produces long-term consequences by altering HPA function. (58)

Glucocorticoids influence foetal brain development by altering neuronal migration, synaptic plasticity, and neurotransmitter activity. Because of the positive feedback loop achieved by cortisol secretion and placental CRH, the effects of excess endogenous or synthetic glucocorticoids may have a negative potential for the immature developing foetal brain.(59)
Based on data from animal experiments and ongoing clinical trials, exposure to single or repeated courses of antenatal glucocorticoids influences the foetal and neonatal hypothalamic-pituitary-adrenal axis, but the long-term effects are not fully known. Animal studies indicate that these changes in the HPA axis persist into adulthood. This alteration of the activity of the HPA axis may be influenced by the time of exposure (gestational age) and dependent on the number of doses administered, without showing significant differences between the two substances(41,62,63).

General objectives of the doctoral thesis

The central objective of the research thesis was to follow the postnatal adaptation of newborns extracted by caesarean section, with a gestational age between 36 weeks and 38 + 6/7 weeks and who benefited from the administration of antenatal dexamethasone corticoprophylaxis.

As I presented in the general part of the thesis, cesarean birth involves risks for both the pregnant woman and the newborn, this procedure can involve immediate and long-term complications for both patients. The growing percentage of women who choose to give birth by caesarean section, combined with certain pathologies that require such a delivery method, has determined the increase in the incidence of newborns that require admission to Neonatal Intensive Care Units and support through specific therapies.

Our work aimed to study the impact of cesarean deliveries on the newborn and the evaluation of the frequency of respiratory events in the group of newborns who received dexamethasone during pregnancy versus newborns who did not receive corticophylaxis for pulmonary maturation.

The follow-up of newborns was carried out by evaluating them in the delivery room, respectively in the first 10 minutes of life, later in the Neonatology ward, and included both clinical evaluation, by performing an objective examination, and paraclinical evaluation by monitoring vital functions, measuring gas exchange (arterial ASTRUP), radiographs and cardio-pulmonary ultrasounds.

The general objectives of the research thesis are made up of the following sub-points:

a. Evaluation of the incidence of cesarean births in the population of pregnant women in our Clinic

b. Evaluation of the personal and demographic characteristics of pregnant women who gave birth by caesarean section.

c. Postnatal evaluation (clinical and paraclinical) of newborns extracted by caesarean section from the two study groups

d. Assessment of the need for admission to Neonatal Intensive Care Units and the need for respiratory support

e. Remote evaluation of newborns from the two groups regarding the evolution of neurological acquisitions by age stages.

II.2. Working assumptions

The present theme started from the following working hypotheses:

a. The increased percentage of cesarean births implies a more difficult respiratory adaptation among newborns.

b. Certain predisposing factors, such as: gestational age, lack of labor, gestational diabetes, male gender, twin pregnancy, disrupt immediate postnatal adaptation

c. The administration of glucocorticoids in pregnancies at risk of preterm birth under 34 weeks has beneficial effects on the secretion of surfactant and the respiratory adaptation of the newborn and is the most widely used method of therapeutic prophylaxis worldwide

d. Performing corticoprophylaxis in pregnancies that exceed 35 weeks of gestational age remains a controversial subject, although it is proven that the respiratory adaptation of early term newborns, especially if they are extracted by caesarean section, is often difficult

e. The specialized literature presents points of view that justify and support the administration of glucocorticoids (betamethasone or dexamethasone) among the population in which the birth does not proceed physiologically

f. Finding in the specialized literature some studies regarding the neurological changes that glucocorticoids can generate in the subsequent acquisitions of newborns.

The present study is a prospective observational study. Regarding the argumentation of the notions presented above, the prospective character is defined by the way of including patients in the study, which involved the collection of data on the pregnant woman from the clinical observation sheets, and the information on the newborns was obtained through the clinical assessment in the ward Neonatology. Later, for the follow-up of the newborn regarding the general clinical development and the observation of neurological acquisitions at the age of one month, respectively 3 months of life, the infants were evaluated in the Neonatology office of the Elias University Emergency Hospital.

The study, which was carried out over three years (2017, 2018, 2019, 2020 and 2021), included a total of 222 newborns, of which 81 newborns came from pregnancies with a gestational age greater than 36 0/7 weeks and received antenatal dexamethasone; the other 141 neonates were from pregnancies with a gestational age greater than 36 0/7 but did not receive antenatal dexamethasone. The mode of birth was by caesarean section, in the absence of labor or at its onset.

Study population

The study population was represented by a group of 81 newborns with a gestational age of more than 36 weeks, who were born by cesarean section and who antenatally received corticoprophylaxis with dexamethasone. The control group was represented by 141 newborns with

the same gestational age as those in the study group and who did not receive dexamethasone before birth.

Also, all the pregnant women were evaluated by the Obstetrics-Gynecology specialist and were advised about the risks involved in cesarean delivery both for them and for the newborn. The administration of corticoprophylaxis to pregnant women who gave birth by caesarean section was carried out with the patients being informed about the effects on the fetus and the newborn.

The variables addressed to the newborn were then entered into the database: gestational age, sex, birth weight, APGAR score at 1 minute and at 5 minutes, coloration, presence of respiratory manifestations, Silverman score value, need for admission to Intensive Care , the need to administer additional oxygen - under the cephalic tent, respiratory support/mechanical ventilation, the constants of vital parameters: Sat.O2, AV, BP, parenteral nutrition, inotropic support, antibiotic therapy, surfactant administration, pulmonary radiological appearance, cardiac/pulmonary ultrasound, the number of days of hospitalization.

As far as Romania is concerned, there are no exact statistical data related to the prevalence of cesarean operations. Starting from the observation of the neonatal adaptation of newborns extracted by caesarean section and finding that these patients more frequently need care in Neonatal Intensive Care units, due to the development of respiratory symptoms such as transient neonatal tachypnea, we initially carried out, within the Clinic our a statistical analysis over three years (2017, 2018, 2019), following the evolution of the method of birth. Thus, during the three years studied, the trend is clear, the prevalence of cesarean operations is much higher compared to physiological birth, and not infrequently this method of birth is the option of the pregnant woman, despite the advice given by the Obstetrics-Gynecology specialist about the risks of such an incident.

In addition to the initial study that involved tracking the mode of birth and the postnatal adaptation of newborns in the period 2017-2019, we followed in a prospective study, which involved studying the observation sheets of the pregnant woman and the newborn, the impact that had on the method of birth and immediate postnatal adaptation during the Covid 19 pandemic, respectively in the years 2020-2021.

The inclusion criteria in the study were: pregnant women with a minimum age of 18 years, all pregnant women with a developing pregnancy and a gestational age over 36 weeks, pregnant women with indication of cesarean delivery, patients who gave their consent for antenatal

dexamethasone administration, patients who gave their consent for the inclusion of newborns in the study by signing the informed consent, newborns with a gestational age of more than 36 weeks extracted by caesarean section after antenatal administration of dexamethasone, newborns with a gestational age of more than 36 weeks extracted by caesarean section without antenatal administration of dexamethasone.

Exclusion criteria: pregnant women under the age of 18, pregnant women less than 36 weeks pregnant, pregnant women who gave birth vaginally, premature newborns with a gestational age of less than 36 weeks, newborns with surgical pathologies (e.g. diaphragmatic hernia), severe cardiac malformations.

Dexamethasone administration protocol:

The Obstetrics-Gynecology specialist who monitored the pregnant woman's pregnancy, following regular consultations, advised the pregnant woman about the method of delivery. Thus, when the pregnant woman had contraindications regarding vaginal delivery, the Obstetrics-Gynecology specialist recommended the extraction of the fetus by cesarean section as the mode of delivery.

Thus, pregnant women, who gave their consent for the administration of dexamethasone and who did not receive another corticoprophylaxis treatment during pregnancy, were recommended to carry out the administration in a specialist office or at the family doctor. The administration of dexamethasone involves the administration of 4 doses (6 mg/dose) intramuscularly, at an interval of 12 hours each.

A caesarean section was performed at least 24 hours after the end of the last dose and within a maximum period of 2 weeks after the end of the cure.

When the pregnant woman was already hospitalized for pregnancy monitoring or due to associated pathologies, the dexamethasone treatment was performed in the hospital, and the birth occurred within a maximum of one week after the last administration.

Protocol for monitoring and admission to the Intensive Care Unit of newborns:

The admission of newborns to the Neonatal Intensive Care Unit (NICU) involves risks for the newborns and stress for their families, with a high cost to the health system, so certain criteria must be met to admit a newborn to the NICU.

The first hours of a newborn's life are essential in its further development, even more so for newborns with risk factors or ante- or perinatal events that may endanger their life. Close monitoring of at-risk neonates is therefore crucial, and after NICU admission the first few hours are critical for high-risk neonates in general. The entire medical staff is trained in the careful attention to detail in the delivery room and during the first hours after birth that is necessary to avoid some of the immediate and long-term complications.

In general, the full-term newborn, who has not suffered complications during labor or delivery, or who does not have certain life-threatening pathologies, does not experience difficulties in the immediate postnatal adjustment.

However, the newborn delivered by caesarean section, especially if this happens in the absence of the onset of labor, may present certain clinical manifestations that require admission to Neonatal Intensive Care units, monitoring and the institution of supportive intensive treatment.

For all newborns extracted by caesarean section, in the first hours of life, possible signs and symptoms of respiratory distress were monitored. In some cases the symptomatology was evident from the delivery room and then the newborn was admitted directly to the NICU, but in other situations the symptomatology was accentuated in the first hours of life.

The clinical signs observed in the newborn were:

- Coloration (rosy/acrocyanosis/pale/cyanotic)
- Capillary refill time
- Silverman score (expiratory moaning, throbbing of the nasal passages, intercostal, subcostal draft, xiphoid congestion)
- Presence of vesicular murmur in both lung fields
- Detection of superadded rales
- Detection of heart murmurs
- Muscle tone
- Reactivity

Once admitted to the Neonatal Intensive Care Unit, all newborns had the following laboratory analyses:

- Blood group, Rh, TCD;
- Hemogram;
- Arterial blood gases (ABG)

- Blood sugar
- +/- C-reactive protein
- +/- Blood culture

The following vital parameters were monitored in dynamics:

- Temperature (intrarectal);
- Oxygen saturation (SpO2) - preductal;
- Ventricular allure (AV);
- Blood pressure (BP);
- Respiratory frequency;
- Intestinal transit ;
- Diuresis.

Additionally, depending on the evolution of the newborns, clinical monitoring and laboratory analyses, the following paraclinical investigations were performed:

- Cardio-pulmonary X-ray from anterior-posterior incidence;
- Pulmonary ultrasound;
- Cardiac ultrasound;
- Transfontanel ultrasound.

The presence of functional respiratory syndrome, the need for admission to the NICU department, the number of days of hospitalization were the parameters monitored in both groups of newborns, both those extracted by caesarean section and who received antenatal dexamethasone, as well as those who did not dexamethasone, but the mode of delivery was cesarean.

The protocol for monitoring newborns after discharge:

Starting from international studies that draw attention to the possible changes that glucocorticoids produce in neurocognitive development, under the guidance of neonatologist colleagues specializing in paediatrics, we followed in the neonatology office of the "Elias" University Emergency Hospital Outpatient Clinic, in stages of age, children who received antenatal dexamethasone, compared to those in the control group.

Follow-up of newborns was difficult to achieve because most patients did not come to the office, most likely being followed and evaluated by family doctors or paediatricians.
Thus, information related to the evolution of these newborns in infancy was difficult to obtain and there was no consistency in monitoring, and the number of children followed was small.

The parameters we monitored together with the pediatricians were: growth curve, motor acquisitions characteristic of the age stages (supporting the head in a vertical plane, support on the forearm in the prone position, rolling over, turning from one side to the other, maintaining the sitting position without support), cognitive-behavioral language, expressive language (recognizes voice, recognizes parents' faces, coos, smiles), disappearance of certain archaic reflexes (Moro reflex).

When certain changes were observed in the neurological evolution of any infant, regardless of whether they received antenatal dexamethasone or not, they were referred to a specialist consultation with a pediatric neurologist for a thorough evaluation and possible diagnosis.

I mention that in the group of newborns followed by us, there were no situations that required the evaluation by the specialist Pediatric Neurologist, the infants having a normal clinical evolution during the period in which they were consulted in our office.

On the other hand, the limitations of the study were given by the lack of consistency in the assessment of these infants

Personal contributions

We conducted a study to follow the postnatal adaptation of neonates extracted by caesarean section, with a gestational age between 36 weeks and 38 + 6/7 weeks and who benefited from the administration of antenatal dexamethasone corticoprophylaxis.

The study included a group of 81 newborns with a gestational age of more than 36 weeks, who were born by cesarean section and who antenatally received corticoprophylaxis with dexamethasone. The control group was represented by 141 newborns with the same gestational age as those in the study group, but who did not receive dexamethasone before birth.

In the present study we demonstrated a statistical correlation between the administration of corticoprophylaxis and the improvement of adaptation immediately post-anal, but at the same time we observed that there are also risks, such as the manifestation of neonatal hypoglycemia, and over time, it can cause an impairment of neurocognitive development.

Also in the same study, we followed the evolution of the method of delivery, observing an upward trend of cesarean delivery.

Starting from the observations made during the three years of the study, we also performed the statistical analysis of the following two years, 2020 and 2021, which coincided with the pandemic period caused by the SARS-CoV-2 virus. We have noticed that in these years the addressability of pregnant women for medical services has decreased, causing a more difficult evaluation of these pregnant women, so as regards the administration of antenatal corticoprophylaxis, the administration of glucocorticoid courses for pregnant women at risk has decreased. Another observation made brought to the fore the need for care in neonatal intensive care units of newborns from pregnant women during this period, as a greater number of newborns presented with neonatal respiratory distress.

The **conclusions** of our study are unanimous with the results from the literature, therefore we concluded that the administration of corticoprophylaxis in the case of pregnant women at risk at gestational ages greater than 36 weeks of gestation can have beneficial effects on the fetus, by decreasing the incidence of neonatal respiratory distress but the values obtained had no statistical value. Important statistical correlations we observed in the group with dexamethasone and the male gender, which had a higher birth weight. Another statistically significant correlation we found between the degree of respiratory distress and the need for mechanical ventilation or supplemental oxygen delivery in both batches. As for specific neonatal respiratory pathology, the ratio between the two batches was 2:1.The rate of mechanical ventilation in the two groups was equal, with a slight decrease in the number of days of hospitalization in the dexamethasone group. There was also an increase in the number of days of administration of specific TINN medication, namely parenteral nutrition, anti-biotherapy and inotropic support, but all correlated with the degree of respiratory distress and the need for mechanical ventilation.

However, as in any therapy, there are also risks, and neonatal risks can be immediate, through the occurrence of neonatal hypoglycemia, but can also be late, through influencing the hypothalamic-pituitary axis, with the impact of the neurocognitive development of this category of newborns. Therefore, it is important to establish a multidisciplinary team to follow these children at any age, at developmental stages, so that the approach of cesarean section birth and the administration of antenatal corticosteroid prophylaxis has as little adverse effects as possible.

Finally, we noticed in the studied group the upward trend of cesarean delivery. Observation that can have an impact on immediate neonatal adaptation, with the need to care for these newborns in neonatal intensive care units but can also have a considerable impact on the birth rate.

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List of presentation and publication

Oral presentation

- Forum Perinatologia - „What's new about BPD? a review" - 25 martie 2022 – Asist. Univ. Dr. Adriana, Dr. Andreea Luca, Dr. Silvia Adela Constantinescu, Prof. Univ. Dr. Simona Vlădăreanu.
- Forum Perinatologia - Corticoprofilaxia antenatală și beneficiile neonatale în nașterea prin operația cezariană – 26-27 martie 2021- – Asist. Univ. Dr. Adriana, Prof. Univ. Dr. Simona Vlădăreanu.
- Forum Perinatologia - „Particularitățile nou-născutului cu restricție de creștere fetală din terapie intensivă neontală" – 27 martie 2021 – Asist. Univ. Dr. Adriana Tecuci.
- Forum Perinatologia - Stroke-ul neonatal – prezentare de caz – 9 martie 2019 – Asist. Univ. Dr. Adriana Tecuci, Prof. Univ. Dr. Simona Vlădăreanu, Dr. Alexandra Popa

Publication

- Revista Ginecologia.ro – „Is dexamethasone a good idea when we talk about caesarean delivery?" – Asist. Univ. Dr. Adriana Tecuci, Prof. Univ. Dr. Simona Vlădăreanu, Dr. Nicoleta Andreea Luca, Dr. Silvia Adela Constantinescu, Prof. Univ. Dr. Radu Vlădăreanu - 24 martie 2022.
- Revista Obstetrica și Ginecologia - „Types of childbirth nowadays and their impact on both mother and newborn" - Asist. Univ. Dr. Adriana Tecuci, Prof. Univ. Dr. Simona Vlădăreanu, Dr. Nicoleta Andreea Luca, Dr. Silvia Adela Constantinescu, Dr. Dragos Tudorache, Prof. Univ. Dr. Radu Vlădăreanu - 31 octombrie 2022.
- Revista Ginecologia.ro - „Corticotherapy, benefits and risks – literature review" - Asist. Univ. Dr. Adriana Tecuci, Prof. Univ. Dr. Simona Vlădăreanu, Prof. Univ. Dr. Radu Vlădăreanu. Asist. Univ. Dr. Simona Popescu, Dr. Mihaela Bot - 28 septembrie 2018.
- Revista Perinatologie - „Congenital cystic adenomatoid malformation of the lung – case presentation" - Asist. Univ. Dr. Adriana Tecuci, Prof. Univ. Dr. Simona Vlădăreanu, Prof. Univ. Dr. Radu Vlădăreanu, Asist. Univ. Dr. Simona Popescu, Dr. Diana Costache, Dr. Ciprian Pop-Began - 7 mai 2018