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Search term: preterm birth, antenatal corticosteroids, tocolysis

TABLE OF CONTENT

1. INTRODUCTION

Preterm birth, occurring in less than completed 37 weeks of gestation, is associated with serious short-term neonatal complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) and long-term consequences like neurologic impairments.

Therefore, preventive measures are taken to avoid preterm birth as much as possible.

In principle, interventions aiming to prolong pregnancy and to improve neonatal outcome are considered. Systematically preventive measurements can be divided into primary, secondary and tertiary prevention. Primary prevention can be set including general measures. These are addressed to all patients who do not yet have an increased risk of premature birth. Secondary prevention is based on the fact that a higher risk of preterm birth is already known mainly from medical history. It is important to mention that the patients are still asymptomatic. Part of the tertiary prevention is the tocolytic agents, which aim to avoid or inhibit uterine contraction. The intravenous administration of high doses of magnesium for neuroprotection plays an important role in preterm birth. Also, the antibiotic treatment should be mentioned, because ascending infection influence the onset of preterm labor.

The aim of this thesis is to present the antenatal administration of corticosteroids and to briefly mention which other medications are relevant in the context of an imminent preterm birth. As RDS is associated with surfactant deficiency and immature lung maturation, the antenatal administration of corticosteroids is certainly of particular relevance.

New thoughts are about unsolved issues such as dose regiment, about exposure and repetition. The "perfect timing" for the induction of lung maturation remains unclear. Determining a precise interval is especially important in case of repeat dosage to ensure the effectiveness. The dose regimen established by pioneers Liggins and Howie has not been changed since the 1970s. However, it seems necessary to improve these regiment in order to avoid excessive fetal exposure to antenatal corticosteroids and therefore limit potential side effects and moreover long-term effects. The issue is mainly that fetuses are exposed to unnecessary high concentrations of antenatal corticosteroids for the desired maturation effect**.** Repeating the application is also of particular relevance if delivery has not occurred after the initial treatment. A single repetition, a so-called "rescue course" and multiple repeated courses may have different effects. Furthermore, an

alternative route of the application might be considered in order to decrease the associated side effects.

1.1. PRETERM BIRTH

According to the World Health Organization (WHO), approximately 15 million preterm births are registered per year, which means that one out of ten babies are born too early. Preterm births are becoming increasingly common worldwide. Preterm birth is defined as birth before completion of 37+0 weeks of gestation or fewer than 259 days since the first day of woman's last menstrual period (LMP). Determining the Gestational Age is essential defining preterm birth and is provided in completed weeks plus additional days after the first day of menstrual bleeding. Preterm birth can be classified into late preterm (34+0 to 36+6 weeks), moderate (28+0 to 33+6 weeks), very preterm (24+0 to 27+6 weeks) and extremely preterm (<24 +0 weeks) (Schneider H. et al., 2016). The use of GW 22+ 0 also to distinguish between "life birth" (WHO definition) and "preterm birth". There are different ways of estimating gestational age. The simplest is calculating the days since the beginning of the last menstrual period. A reliable method is using early obstetric ultrasound and determining Crown Rump Length (CRL). It is the most common method to estimate the gestational age up to ± 3 days. The individual measurements can be compared to standardized growth curves. Premature births can also be defined by determining the birth weight of the baby. According to WHO, all babies with a weight under 2 500 g are called premature. This specific limit has been chosen based on epidemiological observations which showed that the mortality risk is 20 times higher for babies below 2 500g. It is also important to mention that the Austrian Midwife Law (§8, Abs.1) defines preterm birth, miscarriage and stillbirth. In case of a stillbirth, a complete exit from the womb should be fulfilled, signs of life such as breathing, heart action or pulsating umbilical cord should not be observed and the weight of birth should be 500g or more. Those previously listed criteria are essential to differentiate stillbirth from miscarriage. Stillbirth and miscarriage increase the risk of preterm birth in following pregnancies.

Nevertheless, the definition of preterm birth remains to be a main issue and a uniform definition should be accepted worldwide to improve comparability and statistics.

Risk factors of preterm birth are listed below.

Risk factors	OR	95% CI
e.g. spontaneous preterm birth	3.6	3.2 – 4.0
Pregnancy interval <12 months	4.2	3.0 – 6.0
Pregnant women <18 years old	1.7	1.02 – 3.08
Asymptomatic bacteriuria	1.5	1.2 – 1.6
Vaginal bleeding in early pregnancy	2.0	1.7 – 2.3
Vaginal bleeding in late pregnancy	5.9	5.1 – 6.9
Multiple pregnancies	approx. 6	
Smocking	1.7	1.3 – 2.2

(Leitlinienprogramm DGGG OEGGG SGGG, 2020)

1.2. MORTALITY AND MORBIDITY AS A CONSEQUENCE OF PRETERM BIRTH

1.2.1. RESPIRATORY DISTRESS SYNDROME

The Respiratory Distress Syndrome counts among to one of the main serious adverse effects related to preterm birth and therefore primary leads to early neonatal death and disability.

The incidence of RDS represents 1% in relation to all births but depending on the gestational age, there are significant differences.

The Oxford Vermont Study has shown that the RDS is particularly high, with an incidence of 80% at early premature births, i.e. 26 + 0 week of gestation (Lucey JF et al., 1991). In comparison, in the later stages of pregnancy the percentage of RDS slowly decreases, reaching 60% for 28-30 weeks of pregnancy. Beyond that range, the occurrence of RDS is much less frequent but nevertheless it is still more significant than in term births. Avoiding RDS is therefore one of the main aims in order to decrease significantly the mortality and morbidity rate concerning very immature premature births. But there are other accompanying or secondary diseases which are also responsible for the high mortality rate. The doctor identifies them by looking for typical clinical symptoms like tachypnoea, sternal and intercostal retractions, expiratory groaning and cyanosis that occur immediately after birth. Additionally, intensified recording of the airways in the thorax

image is a typical radiological feature. For early detection of pulmonary diseases, a blood gas analysis is therefore necessary, in order to detect the presence hypoxemia and hypercapnia occur in this case. According Liggins and Howie (1972), “an infant was regarded as having suffered from RDS only if both clinical and radiological signs were present: clinical signs of grunting respirations and chest retraction present during the first three hours and persisting beyond the first six hours after delivery, and a radiological pattern of having fine generalized granularity of lung fields with air bronchogram.”

Aiming to decrease mortality and morbidity, the use of antenatal glucocorticoids indicated in threatened and planned preterm birth and therefore justified by the fact that they contribute significantly to reduce the risk of RDS. Since every medication is of course also associated with side effects, this treatment should only be chosen in the case of a clear risk for a RDS.

1.2.2. INTRAVENTRICULAR HEMORRHAGE

IVH is known as bleeding inside or around the ventricles in the brain.

This complication occurs in the first several days of life. It is known that prematurity, low birth weight and coagulation disorders are certainly the main risk of the occurrence of Intraventricular hemorrhage. Also, it primarily concerns infants with respiratory distress or with other complications. Hypertension or infections in the mother may also be considered as a risk factor. Premature infants are at a higher risk for intraventricular hemorrhage because their blood vessels are less developed and therefore more vulnerable.

Based on the results of CT-scans, the severity of intraventricular hemorrhage can be classified into the four following degrees:

Grade I: hemorrhage in small area of the ventricles

Grade II: intraventricular hemorrhage in less than 50% of the ventricular volume

Grade III: intraventricular hemorrhage in more than 50% of the ventricular volume

Grade IV: hemorrhage in the brain tissues around the ventricles

The first two grades are the most commonly found and involve a smaller amount of bleeding which occurs in a small area of the ventricles or inside the ventricles. For grade 3, ventricles are enlarged by the blood and for grade 4 bleeding occurs in the brain tissues around the ventricles. These two

types of intraventricular hemorrhage are considered to be more severe because more severe bleeding occurs. Long term brain injury is therefore more likely to be associated. Further, an increased amount of cerebral spinal fluid in the brain, hydrocephalus, may result. All in all, adverse neurodevelopmental outcomes in extremely preterm infants are associated with this complication. The symptoms of IVH are apnea, seizures, cyanosis, bradycardia, seizures, anemia. It is noticeable that these symptoms are also associated with other complications like RDS. For the diagnose of IVH, a cranial ultrasound is used and therefore the amount of bleeding can be properly graded.

1.2.3. NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) is a major comorbidity and surgical emergency associated with prematurity and is an inflammatory bowel disease that usually affects the terminal ileum or ascending colon.

It is a devasting gastrointestinal disease associated with sepsis and intestinal perforation.

Low oxygen level is considered as a major risk. In this condition, brain and heart are primary supplied with blood, which results that microcirculatory disorder in intestine. Local ischemia may lead to the necrosis of the intestine wall. This favors the bacteria´s invasion of the wall, which are normally located in the intestine. In fact, bacteria enter the infant's bloodstream through the damaged intestinal wall and cause infection what lastly lead to death. Further, when the entire intestinal wall is damaged and the intestinal wall perforates, the contents of the intestine spill into the abdominal cavity and cause inflammation and usually an infection of the abdominal cavity and the peritonitis.

Necrotizing enterocolitis occurs in the first two weeks of life in infants. Besides intestinal ischemia, bacterial invasion and thus inflammation, enteral feeding plays also a major role in the occurrence of Necrotizing enterocolitis. It has been found that infants fed with breast milk are less likely to have necrotizing enterocolitis because firstly, milk is easier to digest, secondly supports the immune system and lastly helps intestinal cell maturation. Formula feeding should therefore be avoided. Infants preterm born and with low weight have less mature intestines and have therefore problems of digestion. Also, the immune system is not capable facing the infections.

The typical symptoms are bradycardia, apnea, lethargy, oedema, vomiting, diarrhea, abdominal distension, hypotension.

An abdominal X-Ray may be supportive in order to diagnose necrotizing enterocolitis and gas or air in the wall of the intestine, in the veins also in the liver can be observed in this case.
According to the blood test, decrease in white blood counts and platelet have been noted which result with a greater risk of bleeding a serious systemic infection.

1.3. LONG TERM CONSEQUENCES

Preterm birth is also associated with long term consequences such as neurologic impairments such as cerebral palsy.
Children born after very early preterm birth are usually followed up until 6 years of age.
These complications may cause high care efforts and creating high costs both for the family and the community.

2. METHODS

This thesis is based on a literature review and has been conducted from February 2020 until June 2020.

The purpose of the literature research was to evaluate the different treatments in patients at risk of imminent preterm birth. The focus was on the antenatally administration of corticosteroids. Furthermore, other prevention measurements have been included in the research. The standard question was the performance of the involved drugs considering the intended use, as well as benefit-risk balance assessment.

Initially, general medical databases and search systems such as PubMed, Clinical trials.gov or Google Scholar have been used. Additionally, this literature research was based on specialized databases such as Cochrane Collaboration Review Search. The data shall select the clinical data relevant for to the different treatments. General search engines such as Google have been considered to be less relevant because of being less specified. Several books have been found manually in the field of pregnancy and childbirth, pharmacology, endocrinology and biochemistry. All recommendations mentioned are in accordance to the guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Österreichische Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe (SGGG), Prävention und Therapie der Frühgeburt, AWMF-Registernummer 015-025 Leitlinienklasse S2k, Stand Februar 2020 Version 1.1. These sources have been used in order to demonstrate the state of the art in Germany, Switzerland and especially in Austria. Further, WHO recommendations on interventions to improve preterm birth outcomes have been used to point out the worldwide recommendations.

The following search terms have been chosen: (preterm birth) or (antenatal corticosteroid) and „67 218“publications have been found dated between 1964 until 2020. This underlines that this field became of increasing importance.

3. DIAGNOSIS OF PRETERM BIRTH

3.1. PRETERM LABOR

It is important to distinguish between iatrogenic and spontaneous preterm birth. In case of iatrogenic preterm birth, the doctor decides to induce birth or to perform an early caesarean section. Severe pre-eclampsia, intrauterine growth restriction or ascending infection could be managed by iatrogenic preterm birth.

In contrast, spontaneous preterm birth is characterized by the independent occurrence of preterm labor, premature rupture of the bladder or vaginal bleeding.

In order to diagnose preterm birth carefully, the doctor must perceive various symptoms. One of the most important issue is to distinguish false labor from true labor. False labor often affiliated with Braxton Hicks contractions is likely to happen during the second and third trimester.

False labor is characterized by undulating abdominal pain and by hardening of the belly, which seems not very severe and comes and goes with the times. Patients notice that the pain subsides when changing position, resting or stopping physical exercise.

The crucial point is that false labor has no influence on the shortening and opening of the cervix whereas true labor has. To get more into details, the first stage of true labor can be classified into early, active and transitional labor depending on the dilatation of the cervix. Normally the cervix is not dilated during pregnancy in order to prevent infection and inflammation in the uterine cavity. The pain during true labor is about to amplify and intensifies with time. It is therefore more significant compared to perception of pain during false labor. Pain is a subjective outcome and hence often differently rated by women.

3.2. CERVICAL INSUFFICIENCY

Due to mechanisms of infection and inflammation as well as changes of the cellular matrix of the connective tissue the cervix gets wider and therefore this could be a sign of the beginning of delivery. As a consequence, the cervix is getting shorter. Patients in this situation are usually asymptomatic. Presence of cervical insufficiency is often preceeding preterm birth.

3.3. PROM

Especially cervical change must be closely monitored. Cervical insufficiency is diagnosed in case of cervical shortening and dilation.

Preterm premature rupture of membranes (PPROM) occurs before week 37/0 and premature rupture of membranes (PROM) means that the rupture occurred before labor. Preterm, premature rupture of the membranes (PPROM) can also be considered as a main symptom for the diagnosis of preterm birth. Once the amniotic membrane which surrounds the baby, ruptures, a higher risk for intrauterine infection is possible. Early placental detachment, amnion infection syndrome and umbilical cord prolapse are possible complications of PPROM.

Causes of PPROM are ascending vaginal infections in the lower genital tract or polyhydramnios. A polyhydramnion refers to the excessive accumulation of amniotic fluid surrounding the fetus, usually occurs in the middle or late phase of pregnancy and is a severe complication. Due to an augmentation of amniotic fluid the uterine tension increases, hence premature contractions may occur. Additionally, a lack of hygiene and smoking contribute to preterm premature rupture of membranes. Bleeding during the first and second trimester could be a sign of PPROM or can also be considered as a main symptom of preterm delivery. An abrupt vaginal fluid outlet and amniotic fluid discharge from the cervical canal are noticed. With the use of the nitrazin / lackmus essay, a main clinically parameter is the measurement of the pH of the vaginal secretion which is normally acidic. The increase in the vaginal pH value can also indicate premature rupture of the bladder. Infection at the lower part of the amniotic sac is often causing premature rupture of the amniotic membranes. It can be false positively detected by having an intense blue color due to contamination such as infected urine, blood or bacterial vaginosis. In case of PROM it is detrimental to perform digital vaginal exams due to the increase in ascending infection.

3.4. BIOMARKERS FOR DETECTING IMMINENT PRETERM BIRTH

3.4.1. CERVICAL LENGTH

The recommended method for evaluating this is using transvaginal ultrasound in order to measure the cervical length and to evaluate if it is less than the established limit of 2,5 centimeters, because this will indicate that preterm birth could be expected.

3.4.2. FETAL FIBRONECTIN

The most promising biomarker together with determining cervical length in predicting a premature delivery is the fetal fibronectin test (Leitlinienprogramm DGGG OEGGG SGGG AWMF-Registernummer 015-025 S2k Version 1.1, 2020). Fetal fibronectin is a structural protein located between the amniotic sac and the lining of the mother´s uterus and is essential for their junction. Once fetal fibronectin above a certain cut-off is detected in vaginal fluid, the body of the mother signalize getting ready for delivery. It is usually found after 36 weeks, so if an increase of fibronectin happens to be above a cut-off of > 50ng between 22 and 35 weeks, a preterm birth is likely to happen. In case of a negative result a premature birth can be ruled out with high certainty, even if other symptoms would suggest it. This is very convincing and contributes to distinguish between women who are actually expecting a spontaneous preterm birth and those who are not.

3.4.3. CARDIOTOCOGRAPHY (CTG)

To evaluate the intensity and duration of contractions a CTG is a commonly used method for the simultaneous recording of the heartbeat frequency of the fetus and registration the activity of contractions of the pregnant woman. It is used to monitor the wellbeing of the fetus and to detect any oxygen deficiency. Cardiotocography lasts around thirty minutes and is usually performed during late pregnancy and during delivery. The baby´s heartbeat is normally recorded externally via the mother's belly using ultrasound and can be measured directly during birth after the amniotic sac has been opened by attaching an electrode to the child's head. This is useful to make sure that no oxygen deficiency for the fetus is detected during labor. Due to this record the physician also examines the well-being of the baby.
However, other examinations have to take place in order to make an adequate diagnosis.

3.5. OTHER EXAMINATIONS

Doppler sonography is an ultrasound method to examine the blood flow focused on the vessels of the fetus. Another method is the kineto-CTG (Cardiotocography) where additionally the movement of the unborn child is recorded. Taking in consideration that the increase of the movement is related to a high oxygen rate, this method visualizes if a deficiency of oxygen could be detected.

It is necessary to use all reliable tests to evaluate the risk of preterm birth. Therefore, incorrect evaluation of the symptoms can have a serious influence on the course of the pregnancy and the up-coming treatment of the mother.

4. PRIMARY PREVENTION

Primary prevention consists in preventive measures for all women before and during pregnancy.
It is a strategy which involves several measurements focusing on the stabilization of the future mother´s living conditions in order to reduce the risk of preterm birth. The aim is further to assure pregnancy care and reduce any insecurities or fears related to this life change.
Education and information about possible physiological and psychological changes are of particular importance for prenatal care and an essential part of each individual screening.
This also includes advice on a lifestyle adapted to the pregnancy. This helps a pregnant woman to recognize the early symptoms of a disturbed pregnancy itself. It should be noted that these pregnant women do not yet show any risks of preterm birth in their medical history.

4.1. LIFESTYLE INTERVENTIONS

With the support of the government and introduction of legally established protective measures, an improvement in living and working situation during pregnancy can be achieved. In Austria, the legal basis is the maternity protection law.
It has been proven that occupational stress is associated with an increased risk of preterm birth (Henriksen et al., 1995; Newman et al., 2001). Heavy work and manual lifting, carrying, pushing or pulling of loads should therefore be avoided.
This also applies to work involving hazardous working conditions. Exposure to biological, chemical or physical agents and work at high temperatures or at night should be avoided too. In a large case-control study conducted in several European countries, it was shown that work performed predominantly in a standing position for more than 42 hours per week is associated with an increased risk of premature birth (Saurel-Cubizolles et al., 2004). However sports activities were not related to preterm birth (Hegaard et al., 2008). Maternal and fetal stress directly stimulates the synthesis of CRH in trophoblasts of placenta and membranes as well as in the decidua, which can lead to increased production of prostaglandines (Lockwood, 1999). It has been suggested that the correlation between chronic stress and preterm birth with a relative risk factor of 1.5 to 2 is relatively low (Hedegaard et al., 1996).

Maternal age at the time of conception is a second independent prognostic factor that must be included in individual risk assessment. Thus, women older than 34 years or younger than 18 years are likely to be concerned.

4.2. NUTRITION

The nutritional status of pregnant women can have an impact on duration of pregnancy and on the birth weight. The pre-conceptional body weight is considerably reduced in the case of chronic malnutrition. It has been demonstrated that the risk of premature birth increases with pre-conceptional malnutrition (Rayco-Solon et al., 2005). Neither isocaloric protein supplementation nor a diet enriched with protein plus calories could reduce the premature birth rate (Kramer & Kakuma, 2003). A low-fish diet is also associated with an increased rate of preterm birth. Omega-3 fatty acids are essential fatty acids and must be consumed in the diet. They play an important role in pregnancy, as they are involved for development of the fetal brain and retina. Biologically most active forms of omega-3 fatty acids are docosahexaenoic acid and eicosapentaenoic acid and omega-3 fatty acids may lead to a prolongation of pregnancy (Olsen et al., 2000). According to a review of the Cochrane Collaboration, the risk of premature birth before 34+0 weeks is significantly lower when fish oil has been taken. A reduced risk of perinatal death and of neonatal care admission may be associated with the omega-3-fatty acid supplementation (Abdelhamid et al., 2018).

A varied diet with high-quality proteins, slowly absorbable carbohydrates and limited fat intake is recommended. Additionally, vitamins, minerals, trace elements, iron and iodine can be taken during pregnancy. Further, folic acid supplementation should already be carried out pre-conceptually. Vitamin A plays a special role in pregnancy. It has been found that a deficiency may contribute to development and progression of lung disease (Timoneda et al., 2018).

4.3. ABUSE OF ALCOHOL AND TABACCO

Furthermore, smocking, illegal drugs such as cocaine and alcohol likely induce preterm birth (Parazzini et al., 2003; Quesada et al., 2012; Shiono et al., 1986)

4.4. INTERPREGNANCY INTERVAL

A short interpregnancy interval, defined as the period between birth and the beginning of the subsequent pregnancy, contributes to an increase in premature birth rate (Agustin Conde-Agudelo et al., 2006). Increased risk of developing PPROM in a subsequent pregnancy is significantly associated with a short interpregnancy interval of less than 12 months (Shree et al., 2018).

4.5. MULTIPLE PREGNANCY

The risk of preterm birth in multiple pregnancy is 6-fold higher compared to singleton pregnancy. Fetal, neonatal and maternal complications may occur more frequently in twin pregnancy (Kiely, 1998; M. V. Senat et al., 1998). Therefore, multiple pregnancy due to assisted reproduction should be avoided by using single embryo transfer.

5. SECONDARY PREVENTION

Secondary prevention focuses on initiating preventive treatments as early as possible for patients with evident risk of preterm birth. It is known that prior experienced preterm birth or uterine anomaly such as a short cervix may increase the risk of preterm birth. However, these pregnant women are still asymptomatic, as neither preterm labor, bleeding nor a preterm premature rupture of membrane were evident.

These following interventions including pharmacological treatments, a surgical procedure and further measurements can be used in order to prevent preterm birth in patients with identified risk factors.

5.1. PROGESTERONE

Progesterone is according to its name a pro-gestational steroid hormone and is produced by the corpus luteum in early pregnancy and at 7 to 9 weeks of gestation by the placenta.

It is essential for the establishment of a successful pregnancy by contributing to the decidualization of the human endometrium. It is essential for the maintenance of pregnancy by promoting myometrial relaxation. This occurs due to a reduction of gap-junction formation. Also, through its binding to the nuclear progesterone receptor (PR) isoforms PR-A and PR-B in uterine myometrium cells, the gene expression of contraction-associated proteins such as calcium channels or oxytocin receptors is inhibited. The production of oxytocin, a hormone involved in uterine contraction and in lactation, is also decreased after progesterone exposure. Additionally, it has been found that this steroid may have anti-inflammatory actions by inhibiting myometrial cell responsiveness to pro-inflammatory stimuli (Wilson & Mesiano, 2020).

According to the World Health Organization (WHO), the administration of progesterone is indicated for women with singleton pregnancy and who have already experienced spontaneous preterm birth. It can be performed in gestational week (GW) 16 + 0 until GW 36 + 0.

Prophylactic use of progesterone to prolong gestation has been confirmed for women who already experienced preterm birth (Meis et al., 2003). Women with a short cervical length may also benefit from the administration of progesterone. It has been reported that the incidence of preterm birth

was significantly reduced after progesterone exposure in asymptomatic women with a singleton pregnancy and a short cervical length on ultrasound of ≤ 25 millimeters before 24 weeks of gestation (Kuon et al., 2019).

It has been found, that the risk of preterm birth is decreased when progesterone has been administrated vaginally. Also, perinatal outcomes in singleton pregnancy has been improved(da Fonseca et al., 2003). The administration of progesterone before 32 weeks of gestation was associated with a reduced incidence of RDS and NEC in the newborn (Rode et al., 2009). This treatment may also lead to a reduction of perinatal mortality rate in asymptomatic women with singleton gestations and who have already experienced spontaneous preterm birth (Boelig et al., 2019). Regarding long-term effects of progesterone, no deleterious neurodevelopmental effects in childhood has been found (da Fonseca et al., 2003). However, it remains necessary to collect more data in order to detect any long-term effects.

According to the Cochrane Review data, no beneficial effects in case of multiple pregnancies have been observed so far (Dodd et al., 2019)

The administration of progesterone seems also relevant in asymptomatic women with short cervix at midgestation. It has been demonstrated that vaginal progesterone may reduce the rate of spontaneous early preterm delivery in those patients (Fonseca et al., 2007).

It is recommended to administrate 250 milligrams of 17-α hydroxyprogesterone caproate once a week in the muscle of the pregnant women at risk of preterm birth. Alternatively, progesterone can be administrated as oral capsule (100 mg) or as vaginal gel (90 mg) every day. Important to mention is that progesterone is an antagonist for glucocorticoid receptor and may lower the response to oral or inhaled steroids (Chapter 60, Obstetric and Fetal Pharmacology, Giacoia).

Nevertheless, there are no general recommendation of progesterone´s use due to the multifactorial etiology of preterm birth.

5.2. LOW DOSE ASPIRIN

Low dose acetylsalicylic acid (Aspirin®) inhibits platelet thrombocyte synthesis.

The use of low-dose aspirin (50-150 mg daily) may also contribute to a reduction of the risk of preterm birth (Roberge et al., 2012) Low-dose aspirin administration is administrated from the 11 until the 36 weeks of pregnancy (Rolnik et al., 2017).

5.3. CERVICAL CERCLAGE

The incidence of preterm birth is increased when the cervix is shortened or opens too early, showing signs of cervical insufficiency.

Cervical cerclage is a surgical procedure where a suture is placed around the cervix in order to give mechanical support. It is a common treatment in pregnant women with incompetent cervix and ensures the baby´s stay in the uterus. It is performed between 12-14 weeks of gestation and will be removed around 37th week of gestation. This strategy aims to minimize the risk of preterm birth in women considered to be at risk. According Cochrane review data, a cervical cerclage contributed to a reduction of the risk in women at high-risk of preterm birth. The risk of perinatal deaths may also be reduced after this procedure has been performed. This only applies to singleton pregnancies(Alfirevic et al., 2017). However, it remains uncertain if cervical cerclage is in fact more effective than vaginal progesterone administration.

5.4. MONITORING PREGNANT WOMEN AT HOME FOR DETECTING PRETERM LABOR

Home uterine activity monitoring may be supportive in detecting signs of preterm labor in women with an increased risk of preterm birth. Data from monitoring would be sent to the hospital and may support detection and further treatment of preterm birth.

According to the Cochrane Review, is has been demonstrated that the likelihood of preterm birth at less than 34 weeks of gestation was lower in women using monitors. It has been concluded that fewer newborns whose mother used a uterine monitoring at home were transferred to the neonatal intensive care unit. However, monitoring may lead to more unplanned prenatal visits and tocolytic treatments. Lastly, “there is no impact on maternal and perinatal outcomes such as perinatal mortality or incidence of preterm birth” (cited from Urquhart et al., 2017).

6. TERTIARY PREVENTION

Tertiary preventions of preterm birth intend to prolong pregnancy in women already considered to be symptomatic. The aim of the interventions is to improve fetal outcome.
Administration of drugs, such as tocolytic agents, magnesium, antibiotics and lastly antenatal corticosteroids, is of particular importance. The focus is set on the contributing effect of corticosteroids in the induction of lung maturation.

6.1. ACS TREATMENT

Initially, Liggins demonstrated lung maturation in lambs in 1969 and 3 years later Liggins and Howie (1972) pointed out the benefits of the ACS treatment in humans. Particularly, it should be underlined that this therapy is nowadays considered as standard of care in case of preterm birth. Corticosteroids refer to both glucocorticoids and mineralocorticoids but is used as a synonym to glucocorticoids.

6.1.1. WELL-KNOWN MECHANISM OF ACTION OF GLUCOCORTICOIDS

The adrenal cortex is an endocrine gland which synthesizes and releases steroid hormones such as glucocorticoid, mineralocorticoid and androgen. Glucocorticoids are synthesized in the zona fasciculata corresponding to the middle layer and they mainly influence metabolic processes and defense mechanisms. The most effective representative is cortisol which is also known as hydrocortisone. The inner layer, zona reticularis, is primary responsible for synthesis of pro-androgen, whereas in the external layer mineralocorticoid synthesis takes place. Daily production of aldosterone is about 100 μg and plasma concentration is 300 pM, which is clearly below that of cortisol (Förstermann et al., 2013)
Glucocorticoids are essential for life and have to be constantly synthesized by glands in a circadian manner in response to physiological cues and stress. The synthesis of cortisol is regulated by the hypothalamic-pituitary-adrenal cortex axis. Inputs from the suprachiamiatic nucleus (SCN) and thus stimulation of the para-ventricular nucleus (PVN) of the hypothalamus is the initiating step. As a consequence, this specific area of the hypothalamus releases corticotrophin-releasing

hormone (CRH) and arginine vasopressin (AVP) which stimulate and activate corticotrope cells located on the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH). The final step is the following activation of the adrenal cortex due to ACTH to synthesize glucocorticoids. Cortisol released by the adrenal cortex has a negative feedback inhibiting effect respectively on synthesis and on secretion of CRH and ACTH in the hypothalamus and anterior hypophysis.

CRH and ACTH release shows a maximum in the early morning. The circadian rhythm of cortisol production is stable and adapts to the day-night rhythm. There are two main types of cortisol secretion, namely the circadian rhythm of basal secretion and strong stimulation of secretion during stress which can be ten times higher than the basal one.

Under severe stress conditions for example in case of infections, hypoxia, narcosis, hypoglycemia, pain or operations there is a strong increase in the release of ACTH. Metabolic, anti-inflammatory and immunosuppressive effects caused by increased cortisol release represent an important mechanism by which the body ensures homeostasis in stressful situations. The body has the ability of adapting to certain stress inducing triggers and in case of their long-lasting exposure the increased secretion of glucocorticoids will be consequently throttled.

Once released in the blood circulation, glucocorticoids have an essential impact on the metabolic system, more precisely in the carbohydrate metabolism. They have an anabolic action of use because of inducing gluconeogenesis out of amino acid in the liver. An increased glucose peak is therefore observed in the blood and there is a decrease of insulin sensitivity while taking glucocorticoids. Rapidly energy sources such as glucose are supplied to the brain and the heart. A katabolic action of use such as proteolysis in muscles, in lymph tissues and in the bones has been proved. In fatty tissue lipolysis can be induced. Adrenalin also leads to fat reduction which can only take place in order cortisol is present. A prolonged use of glucocorticoid induces redistribution of the fat tissue. This is characterized by a loss of fat tissue in extremities and a central gain. Cortisol has additionally an affinity to mineralocorticoid receptor in the renal tubule epithelial cells. These effects are not relevant because cortisol is quickly deactivated by the enzyme 11β-hydroxysteroid dehydrogenase type 2. The mineralocorticoid effect is practically abolished in synthetic corticosteroids. Corticosteroids are profoundly influencing the immune system, which make them one of the most commonly prescribed drugs in the world in case of the treatment of allergic reactions, autoimmune diseases such as rheumatic inflammation. Corticosteroids have in higher doses an antiphlogistic mechanism of action and regardless of the triggering noxious agent, glucocorticoids locally inhibit not only early like oedema, capillary dilatation, fibrin deposition,

migration of leukocytes but also late inflammatory reactions (Förstermann et al., 2013). These hormones have different mechanism of action related to the tissue selectivity. For instance, an increase of excitability of the brain has been found. Less frequent are euphoria, restlessness, increased motor activity and sleep disorder, depression and dysphoria. A hypokalemia, a hypocalcemia, a hypernatremia and an increase retention of water are due to the mechanism of action of the mineralocorticoids in the different parts of the kidney. They improve responsiveness of adrenergic receptors of the smooth musculature of the vessels especially of the heart and of the bronchia for catecholamine (Förstermann et al., 2013)They lead to a change of different types of blood cells particularly an increase in the number of platelets and granulocytes in the blood, whereas number of circulating lymphocytes, monocytes as well as eosinophilic and basophilic granulocytes decreases. The focus here is on the fetal lungs, where they have a significant influence on the production of surfactant.

6.1.2. NUCLEAR EFFECT OF GLUCOCORTICOIDS

Due to its lipophilic property glucocorticoids have the ability of passing through the cell membrane and hence having an intracellular mechanism of action. They bind to a cytosolic receptor which is usually in a complex with heat shock proteins such as Hsp 90 or Hsp 70 and are therefore inactive. But after cortisol binding, the glucocorticoid receptor is released from the complex due to a conformational change. The glucocorticoid-glucocorticoid receptor-complex migrates into the cell nucleus where it influences transcription of several genes. As a dimer, this complex binds to a specific glucocorticoid receptor recognition sequence on DNA namely glucocorticoid response element (GRE). After binding, a number of co-activators such as histone acetyltransferase (HAT) and various members of the chromatin remodeling (CRM) complex are recruited. Then, after the acetylation of histones and the reorganization of the chromatin structure, the binding of polymerase II holoenzymes can now be achieved. This increases the transcription of the respective target genes (Freissmuth et al., 2016). This transactivation by direct binding of the ligand-active glucocorticoid receptor to specific DNA elements is the basis for glucocorticoid-induced metabolic effects. An increased activation of phosphoenolpyruvate-carboxy kinase and of the glucose-6-phosphatase has been found. As a monomer, the glucocorticoid-glucocorticoid receptor complex interacts with other transcription factors such as the pro-inflammatory NF-κB. NF-κB is also located in the cytosol of lymphocytes usually found in a complex with an inhibitor IκB. Glucocorticoid-receptor

complex suppresses the transcription of the NF-κB target gene by binding on the factor´s subunit. NF-κB target genes are mainly genes from proteins which have a considerable influence in the immune-reaction and inflammatory-reaction like for example cytokines, growth factor and cell adhesions molecule. Furthermore, glucocorticoids induce transcription of the inhibitor IκBα and prevent therefore the mechanism of action of NF-κB (Müller-Esterl Werner, 2011). But in high concentration, glucocorticoids may also have a non-genomic effect which is unlike to genomic effects very rapid because of not interfering in the protein synthesis(Freissmuth et al., 2016).

6.1.3. BIOSYNTHESIS OF GLUCOCORTICOIDS

Steroid hormones such as glucocorticoids, mineralocorticoids and sexual hormones are synthesized from cholesterol, which consists of 27 carbon atoms.

Biosynthesis of steroid hormones starts with a deletion of 6 carbon atoms from the side chain of cholesterol. Hydroxylation on position C20 and C22 take place and then a lyase reaction follows. Desmolase cleaves the bond C20 C22 and forms the keto group at C20. This new molecule is called pregnenolone and consists now of 21 carbonic atoms. The speed determining step is the conversion of cholesterol into pregnenolone by the cholesterol desmolase CYP 11A1. Under the influence of 3β hydroxysteroid dehydrogenase (HSD) and CYP 17 which is specifically expressed in the zona fasciculata, pregnenolone is converted to 17 hydroxy progesterone. More precisely, an oxidation reaction of the 3-hydroxy group to a 3-keto group and an isomerization of delta 5 to a delta 4 double bond are following. Progesterone has been synthesized and is then the precursor for the steroid hormone synthesis. If, in one hand, the hydroxylation of progesterone follows selectively at C21, C11 and C 18 by 21-hydroxylase, 11-β-hydroxylase and 18-hydroxylase in the respective order, then corticosterone has been synthesized. Due to an oxidation of the C18 methyl group to an aldehyde, corticosterone converts to the prototype of a mineralocorticoid, aldosterone. If hydroxylation takes place previously at C17, progesterone turns to 17 hydroxyprogesterone which again due to 21 hydroxylase (CYP21) and 11β-hydroxylase (CYP 11B1) respectively, turns to cortisol, the main glucocorticoid. Specific functional group or chemical characteristics are essential for the mechanism of action of cortisol and therefore a tiny modification in a single position may have an enormous impact on the therapeutic effect. A keto-group in position C3, a double bond between C4 and C5, a ketol-rest on C20 and a hydroxy-group at C11 and C21 are found in cortisol. Cortisone and prednisolone have a keto group at position C11 instead of a hydroxy group and are

therefore inactive. The semi-synthesis of corticosteroids is also based on cholesterol. The chemical modification of the natural corticosteroids had the aim to increase the anti-inflammatory, immunosuppressive and anti-allergic effects and to decrease the physiological effects. A separation of the therapeutically desired effect from the glucocorticoid effect has not been successful so far, however, it was possible to achieve a strong reduction of the mineralocorticoid effect as well as an increase of the antiphlogistic effect (Förstermann et al., 2013).

6.1.4. ROLE OF ENDOGENOUS GLUCOCORTICOIDS AT THE END OF PREGNANCY

At the end of pregnancy an increase of glucocorticoids in maternal circulation which is up to 4 to 5-fold higher than in the fetus has been shown (Goldkrand et al., 1976; SIPPELL et al., 1981). This change has crucial impact on maturation of different organs of the fetus and also on the triggering of labor (Thorburn et al., 1977). By the second trimester fetal pituitary adrenal axis is mature and fully functioning. Firstly, not only fetal hypothalamus but especially human placenta secretes corticotropin releasing hormone (CRH) which stimulate the production and secretion of adrenocorticotropin hormone (ACTH) from the fetal pituitary. ACTH in turn stimulates the secretion of cortisol which has an important role in maturation of fetal organs, especially the lung. Placental CRH may therefore be considered as a potentially important promoter of fetal organ development. Cortisol then interacts with glucocorticoid receptors found in human trophoblast, which are the outer layer of a blastocyte significantly developed in the placenta. Glucocorticoids play an important role especially towards the end of pregnancy. This is not only important for the organ systems but also for the triggering of labor pains. For example, glucocorticoids are of particular importance for the beginning of delivery (Li et al., 2014). Also, placental ACTH stimulated the secretion of DHEA-S by the fetal adrenal. Starting from this precursor, estradiol is synthesized in the placenta by aromatization and dehydration. The parallel increase of estrogen to glucocorticoids found in the mother, fetus and in the amniotic fluid is typical in late pregnancy (Blankstein et al., 1980; Carr et al., 1981; Murphy, 1982). Estradiol in turn induces the synthesis of low-density lipoprotein (LDL) and cholesterol in the fetal liver, which is ultimately the basis for cortisol synthesis. Glucocorticoids are involved in prostaglandin synthesis in the amniotic chorion and is therefore of particular importance in the birth process. Fetal cortisol may be involved in

triggering delivery, because cortisol causes a change in steroid genesis in placenta from progesterone to estrogen (Liggins et al., 1977). Estrogen in turn leads to the production of PGF2α in uterine tissue and to the secretion of ubiquitous uterotonic PGE2 by the placenta or fetal membranes during the prelude to labor, which therefore activates the myometrium and initiates delivery. Glucocorticoids do not themselves appear to induce contractions of the myometrium (Schneider et al., 2016).

6.1.5. LUNG DEVELOPMENT AND THE INFLUENCE OF ACS IN LUNG MATURATION

Lung development lasts from the embryonic period through the fetal period to birth and is only completed in the middle of the second year of life. During development in the womb, the lungs undergo major changes in shape and physiology. Lung maturation can be divided into 5 major stages: embryonic, pseudo glandular, canalicular, saccular and alveolar. Embryonic phase begins 3 weeks post conception and development of the first generation subsegmental bronchi takes place. This is followed by the pseudo glandular phase with development of the remaining non-respiratory part of the bronchial space including the terminal bronchioles. An essential step in the lung development is the lining with epithelial cells type I and II, which characterizes the canalicular phase. Type I pneumocytes are flattened cells which leads to minimizing diffusion distance for respiratory gases and therefore facilitated gas exchange between alveoli and the capillaries. Type II pneumocytes can proliferate and differentiate into type I, if required. The other type of pneumocytes are cuboidal and contain many granules in order to story precursor to pulmonary surfactant, which is continuously released by exocytosis. In the saccular phase, vascularization of the areas of the terminal sacculi intended for exchange occurs. Until birth, 20 million saccules are formed. These sacculi finally mature in alveoli after birth, this is the so-called the last part of lung maturation, the alveolar phase (Helmer & Schneider, 2016). It can be considered that the lower alveolar number of a premature baby may be responsible for a respiratory dysfunction. Another function of the alveoli is the production of surfactant which is a complex mixture of lipids, namely glycolipids (approx. 5%) and phospholipids (approx. 85%), and apoproteins (approx. 10%), the main constituents of which are dipalmitoyl phosphatidyl choline (DPPC), phosphatidylglycerol (PG) and apoproteins A, B, C and D. This surfactant is stored in alveolar type II epithelial cells.

The phospholipids lead to a reduction of the surface tension whereas surfactant proteins regulate surfactant function and its metabolism. SP-A not only influences surfactant structure and metabolism, but plays a major role in immune defense such as SP-D. The other two apoproteins SP-B and SP-C, which are hydrophobic membrane proteins are primary responsible for the formation of surface films (Philip L. Ballard & Ballard, 1995).

It is necessary to reduce the surface tension in order to keep the alveoli open which enables an effective gas exchange. As a surface-active substance, surfactant acts like a film covering the epithelial surface of the pulmonary alveoli, thereby leading to a reduction in the alveolar surface tension. Due to its amphiphilic property, it further maintains stability during exhalation to prevent the alveoli from collapsing and the epithelia from sticking together during exhalation characterized by a high surface tension. Alveoli would collapse after each exhalation without surfactant. A sufficient number of mature alveoli which produce surfactant is necessary in order to ensure adequate breathing. Although the alveoli are already developed, surfactant alveoli are only formed in sufficient quantities from the 36th week of pregnancy. Therefore, the main issue for infants born before the 37th week of gestation is, that they are likely having a quantitative lack of surfactant, which may predispose them to RDS.

Glucocorticoids enhance structural and functional maturation of the lungs. They induce the development of pneumocytes type I and II, due to an enhancement of alveolar differentiation. Most importantly, effects on the surfactant system have been found after exposure to synthetic corticosteroids. Due to the administration of ACS, maturation of the type II pneumocytes has been accelerated. As a consequence, an increase in the production of alveolar surfactant protein and phospholipids have been noted after the treatment. An increase of surfactant is additionally found due to higher rate of proteins needed for the phospholipid synthesis required for the production of surfactant. These observations are underlining the intracellular mechanism of action of free glucocorticoids which once passed through the membrane of pneumocytes type II are interacting with a special glucocorticoid-receptor. This complex moves to the nucleus where it interacts with a specific DNA sequence so called GRE, glucocorticoid response element, and enhance the transcription of the genes corresponding to different proteins essential for the synthesis of phospholipids (Liggins & Howie, 1972)

Therefore, synthetic corticosteroids stimulate activity of major enzymes such as fatty-acid synthase, choline phosphate cytidylyltransferase catalyzing the phospholipid synthesis. A

significant increase in tissue and alveolar surfactant production result, which even approached level usually observed at term (Liggins & Howie, 1972).

This improves lung compliance, which is a measure of lung extensibility. Surfactant leads to reduce the lung's tendency to collapse inwards.

Further, Ballard and Ballard demonstrated that corticosteroids have further biochemical effects besides increasing relevant enzymes of the surfactant system. According to data from animal studies, it has been found that corticosteroids enhanced fetal lung antioxidant enzymes including superoxide dismutase, catalase and enzymes of the glutathione redox cycle. Thus, oxidative damage such as hyperoxic acute pulmonary injury can be prevented. In preterm animal expression of the antioxidative enzymes is lower than in animals born at term. This underlines once again the importance of the admission of corticosteroids in improving respiratory outcome in neonates. Also, corticosteroids induce the synthesis of proteins, such as epithelial sodium channel and the membrane protein sodium/potassium ATPase, regulating ion and fluid flux and therefore influencing the clearance of lung fluid from airspaces. ACS treatment lead to an increase of tissue and alveolar surfactant production, improved lung compliance, enhanced clearance of fluid from the lungs and stimulated maturation of parenchymal structure. It has been demonstrated that glucocorticoids may have physiological and biochemical effects in other organs (Philip L. Ballard & Ballard, 1995)

In earlier days determination of lung maturity has been carried out with various diagnostic tests using amniotic fluid samples. A possibility to diagnose maturation of the lungs was to determine the lecithin-sphingomyelin ratio (Gluck et al., 1971). Nowadays it is well known that in gestational ages from beginning of fetal viability until week 33 + 6 because of an insufficient production of surfactant production lung maturation has to be undertaken in all circumstances of imminent preterm birth.

6.1.6. RECOMMENDATION OF THE ADMINISTRATION OF ACS

In 2015, the World Health Organization (WHO) lists and evaluates recommendations for the treatment of antenatal corticosteroids in order to clarify when the use is appropriate.

The therapy can only be carried out, when measures for the recognition of a premature birth are available. What counts here is the accurate assessment of the gestational age and the safely management of preterm labor. Adequate treatment after birth should also be available such as thermal care, feeding support, infection treatment and safe oxygen use.

The intervention is recommended for women from 24-34 weeks´ gestations at risk of preterm birth considered to be imminent. This applies for premature single or multiple birth.

Taking under consideration that glucocorticoids are having an immune suppressive effect, concerns have been raised about their administration in the settings of a premature rupture of the membrane which lead to an increased risk of infection. However, the NIH Consensus Conference clearly underlined that the benefits of the treatment outweigh the potential risks. Thus, the World Health Organization recommends that women 24-34 weeks´ gestations with preterm premature rupture of membranes (PPROM) should also receive this treatment only if clinical signs of maternal infection are absent.

Also, according to the World Health Organization, women with hypertensive disorders are at risk having a premature delivery and the use is also appropriated in that case. In the setting of HELLP, changes such as hemolysis, elevated liver enzymes, low thrombocytes are found. It has been shown that the administration of antenatal corticosteroids was certainly beneficial. Corticosteroid administration was not only antenatal but also intrapartum and postpartum with a dosage of 10 mg in an interval of 12 hours (Woudstra et al.2010). A rapid correction of the liver enzymes, of platelet count and of urinary output which may contribute to a reduction of maternal morbidity may occur due to the postpartum treatment. An improvement of the maternal platelet count and liver function has been noticed by using a short course of high dose of corticosteroids and underlines once more the prophylactic treatment in this special setting (Tompkins and Thiagarajah, 1999, Isler et al., 2001).

For women with pre-gestational and gestational diabetes accompanying intervention should be provided in order to optimize blood glucose control, when they are at risk of preterm birth.

Additionally, the administration is also recommended for women with growth restricted fetus. Greater survival and less disability due to maternal corticosteroids has been demonstrated in a

cohort study (Magann et al., 2017). These beneficial effects may support the use of corticosteroids. Dexamethasone is usually used in case of a rapidly decreasing number of thrombocytes (<50. 000). These mentioned recommendations are evaluated as “strong recommendation” by the World Health Organization in order to improve the health outcome of the newborn.

Patients with preterm labor activity, having a cervical length more than 30 mm or of 15-30 mm and who have tested negative using the fibronectin test, the phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) test or the placental alpha microglobulin-1 (PAMG-1) test should not receive an application of antenatal steroids (Leitlinienprogramm DGGG OEGGG SGGG, 2020).

In case of multiple pregnancies, the effect on RDS is considered to be less than in singletons but ACS is still considered beneficial. However, the preventive use of glucocorticoids is not yet clearly proven due to a lack of clinical evidence.

Finally, the therapy is not recommended for women at late preterm, 34 to 36+6 of pregnancy for whom caesarean section is planned. Also, for women having chorioamnionitis and expecting preterm delivery this treatment is not recommended. ACS administration is contraindicated for women having systematic infections including tuberculosis. (Miracle et al.,2008).

6.1.7. RANGE OF THE ADMINISTRATION OF ACS

According to the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) Guidelines, there are different procedures of the treatment of pregnant women related to the course of pregnancy.

In observational studies, there is an association between fetal lung maturation and higher survival rates already at 23 weeks of gestational age, but this does not necessarily indicate the efficacy of the given drugs.

Worldwide, medical societies set up a grey area according to gestational age in order to define appropriate recommendations on treating extreme preterm infants. In consideration of the individual circumstances and in consultation with the parents, both a curative or a primarily palliative approach are considered being justified after informing about mortality and morbidity numbers of the individual center.

In Austria, the lower limit for possible curative treatment is set at 23 + 0 to 23 + 6 letting the mother or couple decide if active treatment or palliative treatment in this particular week should be considered.

below 22 + 6 weeks of pregnancy

In this extreme early period, keeping these children alive is very challenging. Medical measures in this stage are therefore generally considered to be of little hope.

23 + 0to 23+6 weeks of pregnancy

Curative treatment is only performed if the mother decides for it after receiving the appropriate information.

24 + 06 to 24+6 weeks of pregnancy

During this period of pregnancy, an increase to over 70% of the survival rate of treated premature infants has been observed.

But, Hayes et al. (2008) demonstrated no difference of the incidence of NEC and severe IVH between those infants with glucocorticoid admission and the untreated ones, however, outcome data in this gestational age has improved in the meantime. According to Magann et al. (2017), stimulation of functional maturation does not seem accurate because of a yet not sufficiently advanced lung development.

Those very preterm born infants often suffer from serious health problems and require therefore a life-long assistance.

>25 + 0 weeks of pregnancy

Since the chances of survival of threated preterm infants at this age are actually high, a life sustaining therapy should be sought.

Firstly, Liggins and Howie (1972) concluded that outcomes such as perinatal and neonatal deaths of women treated with betamethasone at the period of 23 to 26 weeks of gestation compared to placebo were not different. RDS or IVH did not show a greater incidence between treatment and control groups.

Secondly, a reduction of 52% (OR = 0.45, 95% CI 0.36–0.56) of mortality from birth to discharge has been observed in a systematic review and meta-analysis when ACS have been administrated

from 24 weeks of pregnancy. This underlines a significant benefit of this intervention regarding the neonatal mortality (Park et al. 2016).

In general, the use of glucocorticoids before the 24th week of pregnancy is acceptable as it may have an improvement of survival. However, it should not be forgotten that survival may also be associated with severe disabilities.

Until 34 + 6 weeks of pregnancy

It is generally recommended to administer ACS between 24 + 0 and 34 + 6 weeks of pregnancy. A decrease of IVH and mortality has been found between 24 + 0 and 28 + 6. (Helmer & Schneider, 2016). A significant reduction in RDS, IVH, and neonatal mortality has been found when glucocorticoids have been administrated between 26 + 0 and 34 + 6 weeks´ gestation (Roberts & Dalziel, 2006).

Beyond 34 + 6 weeks of pregnancy

Since the risk of RDS beyond completed 34 weeks´ gestation is greatly reduced, ACS use in this case is not justified (Helmer & Schneider, 2016).

A placebo-controlled study evaluating pulmonary maturation in late preterm delivery did not find an improvement in respiratory pathologies or a reduction in hospitalization time (Porto et al., 2011)

In ASTECS trial, a significant reduction of RDS was observed in infants born at term due to a 2x 12 mg of antenatal betamethasone administration (2.4% versus 5.1%; RR 0.46 95% CI 0.23-0.93). Over 10 years, half of the mothers were asked to closely observe the psychosocial development and health of their children. In school, those who have had an admission of antenatal corticoids left behind a significantly worse overall impression because significantly more of them were placed in the lower achievement quartile. Due to these observations, antenatal corticoids may have an influence in the psychosocial development and therefore application near appointments should be avoided (Stutchfield et al., 2005). An increase in the rate of cell death in regions of the brain with high mitosis rate was found in animal experiments after corticosteroid treatment (Whitelaw & Thoresen, 2000). A significant growth spurt of the brain is evident near birth; therefore, the antimitotic effect of the glucocorticoids plays a decisive role at exactly this point in time**.**

6.1.8. OPTIMAL TIMING OF THE TREATMENT OF ACS

Defining an optimal timing of the initiation of the treatment is not that obvious.

Liggins and Howie (1972) pointed out that "the functional and morphological maturation of fetal lung occur within 48 hours of glucocorticoid administration." Additionally, they noticed that the beneficial effect of the treatment declines 7 days after administration. The importance of the interval between application and onset of action has been pointed out. The effects of corticosteroids on lungs maturation seem to be reversible and therefore the duration of the exposure is certainly decisive. Actually, an increase of mRNA for surfactant proteins resulting after ACS exposure lasted only 48 hours (Tan et al., 1999).

Further, Liggins and Howie (1972) suggested that the use of corticosteroids seemed to be the most effective when the administration occurred 48 hours to 7 days before birth. Additionally, they noticed that the incidence of RDS is increased 48 hours after the first dose of ACS.

Roberts´ and Dalziel´s meta-analysis in 2006 underlined that the interval between the initiation of the treatment and delivery was contributing to an improvement of the outcome. They determinate an extended interval of 1 to 7 days, which is considered to be the most beneficial. The timing when to administer the medication is therefore particularly relevant for this therapy. (Peaceman et al., 2005) showed an improvement of the ACS use for infants which were delivered less than 7 days after initiation due to a reduced need for respiratory support after birth.

In order to demonstrate that the effectiveness is certainly related to the timing of the initiation of the treatment, Melamed et al. (2015) conduct a retrospective cohort study including 6 870 singleton live-born neonates born between 24 + 6 and 33 + 6 weeks of gestation. The neonates were classified into 4 different groups related to the timing of the treatment: the first group of 1378 neonates were not treated with corticosteroids. In the second group 1473 neonates were exposed to corticosteroids less than 24 hours before birth whereas the third group of 2 721 of neonates the treatment occurred 1-7 days before birth. Compared to the previously mentioned groups, in the last one consisting of 1 298 neonates, the course of corticosteroids was greater than 7 days before birth. It has been concluded that neonates who received corticosteroids 1-7 days before birth, were clearly less likely experiencing bronchopulmonary dysplasia, severe IVH compared to those receiving no

corticosteroids. Furthermore, the odds of IVH were higher when administration occurred less than 24 hours before birth and the odds of mortality and NEC was higher when administration was greater than 7 days before birth. This finding underlined that the treatment is considered to be the most beneficial when administration occurred 1-7 days before birth. The authors also showed that a maximum effect can be observed 24 hours after the administration because earlier severe complications still occur with higher odds. Nevertheless, the worst outcomes have been noted for infants without antenatal treatment (Melamed et al., 2015).

According to the Extremely Preterm Infants in a Swedish Study (EXPRESS) these findings have been confirmed and it has been concluded that the risk for neonatal and infant mortality is twice as high if the therapy has been started before or after the specified interval (1-7 days)(H. Norberg et al., 2017). An increased risk of NEC has been found when the second betamethasone dose has been administrated 12 hours after the initial course. Therefore, a second dose of betamethasone should be given after 24 hours (Khandelwal et al., 2012). Preterm infants, of less than 28 weeks of gestation, born more than 10 days after the first corticosteroid administration had a more than 2-fold higher rate of cerebral hemorrhage (17 % vs. 7 %; OR 4.16, 95% CI 1.59 – 10.87, P = 0.004). A reduction in the rate was achieved by administering a second cycle of antenatal steroids (Liebowitz & Clyman, 2016). Thus, timing of the application of antenatal steroids has a crucial influence on neonatal survival especially for very preterm infants of 26 weeks´ gestation.

According to the most recent data from secondary analysis of two prospective multicenter studies enriched for spontaneous preterm birth, Genomics and Proteomics Network for Preterm Birth Research (11/2007-01/2011) and Beneficial Effect of Antenatal Magnesium (12/1997-05/2004), the association between the optimal timing and the improved fetal outcome has been once again underlined. These data were from singleton women who didn´t received repeated courses and delivered at 23 + 6 to 33 + 6 weeks' gestation. The outcomes according to the various timing of the first dose were reported. The lowest odds of RDS were found when administration occurred 2 to 7 day before delivery. Further, the incidence of severe neonatal and childhood morbidity was particularly increased when ACS exposure was 14 days before delivery (Battarbee et al., 2020).

Knowing that the optimal therapeutic interval is 1 to 7 days after administration, it has been nevertheless observed that only 20-40% of women delivered in that certain period (Adams et al., 2015).

Levin et al. (2016) analyzed closely the optimal timing of ACS administration in different clinical settings. 93% of women in this study were treated with ACS but only in 40% of the cases timing was considered as optimal. Therefore, finding the most appropriated timing remains however challenging. It has been showed that the best timing was found in women with high blood pressure (62.1%) whereas asymptomatic women likely having a spontaneous preterm delivery had a suboptimal timed admission (12%). In certain settings such as PPROM and pre-eclampsia to determinate optimal timing is not that clear due to an important variation of clinical courses. An important issue is that diagnostic tools were not helpful in identifying patients for appropriate steroid timing (Levin et al., 2016).

All in all, these findings point out the importance of administration at a most optimal timing in order to improve not only short term but also long-term outcomes. Nevertheless, it remains unclear when exactly the use of glucocorticoids seems to show the most beneficial effect. Determining a precise interval is therefore important in case of repeat dosage to ensure the effectiveness.

6.1.9. BETAMETHASONE AND DEXAMETHASONE

Synthetic glucocorticoids are used in case of tertiary prevention of preterm birth.

Betamethasone is a synthetic corticosteroid and is also known as 9α-16β-methyl-prednisolone. Its synthesis is based on prednisolone which in turn is derived from cortisol and has an additional double bound in position C1-C2. The synthetic corticosteroids therefore consist of 21 carbon atoms. Betamethasone has additionally a fluoric atom on position 9α and a methyl group on position 16β. The orientation of the group is decisive for the naming of the molecule. Dexamethasone and Betamethasone are epimere, which are special stereoisomers that differ in configuration only in one center of chirality. The two synthetic corticosteroids differ from each other only by the orientation of this methyl group and dexamethasone´s is in turn in position α. Dexamethasone is also known as 9α Fluor 16α methyl prednisolone. However, the introduction of the methyl group increases glucocorticoid like effect. The fluorine atom in position 9 α reinforce also the effect of glucocorticoids (Förstermann et al., 2013). The mineralocorticoid effect is

practically abolished by the addition of the fluorine atom and the methyl group (Freissmuth et al., 2016). The aim of enhancing the glucocorticoid mechanism of action has been therefore achieved.

The lipophilicity of the α side is increased by the fluorine atom. Therefore, this halogen atom contributes to the improved passing through the placenta membrane due to its lipophilic characteristic. Glucocorticoids reach the fetal circulation and have an impact on inducing the maturation of the lungs which is the aim of the treatment. Betamethasone easily crosses the placenta, resulting in a high bioactivity in the umbilical cord, which returns to the reference value within 1-2 days after the last steroid dose (Kajantie et al., 2004).

Betamethasone has an enhanced anti-inflammatory, anti-rheumatic and anti-allergic mechanism of action compared to the endogenous corticosteroid, cortisol. These fluorinated corticosteroids are considered as the standard of care for women at high risk of preterm birth before 34 weeks of gestation.

Celestan biphase, a combination of betamethasone disodium phosphate and betamethasone acetate (1:1), is commonly used in Austria. This drug is an injection suspension containing 3,0 mg of betamethasone-disodium phosphate and 2,7 mg betamethasone-acetate. Cushing's threshold dose is 1.0 mg/die. This threshold refers to the dose of therapeutically applied glucocorticoid above which Cushing´s syndrome is likely to develop. This is especially relevant in case of long-term therapy. An excess exposure to corticosteroids may induce a reduced stimulability or even to an atrophy of the adrenal cortex. In the setting of preterm delivery, 2 ml of Celestan biphase should be administrated intramuscularly. Celestan biphase is not administrated postpartum (Fachinformation Celestan biphase). A quick dephosphorization of betamethasone disodium phosphate leads to a rapid exposure of betamethasone, which is the biologically active form. The highest blood level of betamethasone is reached within 60 minutes and is excreted almost completely after the first day. Phosphorylated steroids rapidly reach high peak levels in the mother and peak levels in the fetus that are about 30% of maternal values (Samtani et al., 2005). A prolonged exposure to betamethasone is due to a slower deacetylation of betamethasone acetate. It is practically insoluble in water and is present in Celestan biphase in the form of microcrystals and is hydrolyzed very slowly at the site of injection, gradually metabolized and excreted. It is still present in the blood in measurable concentrations after 2 weeks. A long-term effect has been noted when betamethasone acetate has been administered, due to a depot formed at the injection site.

Regarding their pharmacokinetic properties, Liggins and Howie (1972) found that the maternal plasma concentration of betamethasone is about 100 ng/ml 1h after the treatment and the fetal plasma concentration is approximately 20 ng/ml within the two hours after treatment. According to Ballard and Ballard (1995), the half-life of betamethasone in fetal plasma is 12 hours, which is twice as high as that in the mother's plasma. The average plasma half-life is about 5 hours, while the biological one is between 36 and 54 hours (Fachinformation Celestan Biphase).
Like other glucocorticoids, betamethasone is metabolized in the liver and excreted via the kidneys. Only 7% and 2% of betamethasone and dexamethasone respectively were metabolized by the enzyme 11β-hydroxysteroid dehydrogenase type 2 whereas, were converted to their 11-keto metabolites (Blanford & Pearson Murphy, 1977). Pharmacologically relevant concentrations may therefore reach fetal circulation.
The orientation is influential, as betamethasone and dexamethasone show pharmacokinetic differences. Because of a shorter plasma half-life, namely 4,5 hours, dexamethasone is commonly administrated as 4 – 6 mg intramuscular injections of dexamethasone sodium phosphate at 12 hours intervals (Brownfoot FC et al., 2013). Contributing to a quicker exposure of corticosteroids is once again the faster dephosphorylation. Biological lifetime of dexamethasone varies from 36 to 72 hours. This prolonged biological activity may be justified by a high distribution volume (Vd=100). In contrast to cortisol, dexamethasone is hardly bound to plasma proteins which leads to an accelerated onset of action compared to cortisol. It is known that only unbound corticosteroids are considered as biological active.

In favor of dexamethasone, the use has been associated with less alteration in fetal heart rate variability (M. v. Senat et al., 1998). But, altered fetal heart rate has not been considered clinically relevant because it is moreover defined as a transient physiological response (Magee et al., 1997; Rotmensch et al., 1999; Subtil et al., 2003). In addition, dexamethasone showed less IVH and shorter length of NICU stay. According the Cochrane review, „the suggestion of increased benefit of dexamethasone over betamethasone from this review for IVH is not sufficient evidence to support dexamethasone over betamethasone“ (cited from Brownfoot et al., 2013).

Dexamethasone has also other advantages which are not related to its pharmacological characteristics. This synthetic corticosteroid is widely available and cheaper that betamethasone. Thus, it is commonly used in low- and middle-income countries (Henderson-Smart et al., 2007;

Saengwaree & Liabsuetrakul, 2005) For betamethasone reduced adverse neurological outcomes at 18 to 22 months have been found. Nevertheless, it remains necessary to perform a randomized clinical trial comparing these two prominent synthetic corticoids in order to predict neonatal or neurodevelopmental outcomes (Lee et al., 2008). A reduced risk of cystic periventricular leukomalacia was additionally found in infants exposed to betamethasone before birth(Baud et al., 1999). Another advantage of the use of betamethasone is, that it was associated with a significant reduction in bronchopulmonary dysplasia according to a retrospective analysis of a US preterm cohort of 334 very-low-birthweight infants, ≤1.5 kg (Feldman et al., 2007). But the effect of these two epimers was similar regarding the reduction of the risk of periventricular leukomalacia in low birthweight (≤1.75 kg) infants (Bar-Lev et al., 2004). According to the Cochrane Review, less maternal chorioamnionitis (RR 0.67, 95% CI 0.50 to 0,90 according 10 studies including 4777 participants) was found when betamethasone has been used compared to dexamethasone (RR 1.35, 95% CI 0.89- 2.05in 5 studies including 769 participants) (Brownfoot FC et al., 2013). But, no difference for maternal death and the incidence of endometritis were reported. Apart from a reduced maternal postpartum length of stay for women who received betamethasone at 12-hourly intervals compared to 24-hourly intervals in one trial (MD -0.73 days, 95% CI -1.28 to -0.18; 215 women), no differences in maternal or neonatal outcomes were seen between the different betamethasone dosing intervals assessed (Brownfoot FC et al., 2013) .

According to recent animal study, lambs exposed to betamethasone-acetate and betamethasone-phosphate required significant lower PIPs after 30 minutes ventilation compared to those exposed the epimers, which in turn improved however dynamic lung compliance and VEI. Lung injury in ventilated preterm infants can be prevented due to a decreased pressure requirement when the combination has been administrated. In the same study, a significant increase of mRNA levels of the surfactant proteins has been found when the combination of betamethasone-acetate and betamethasone-phosphate has been administrated compared to dexamethasone. Similar results in this regard has been found when only betamethasone-phosphate has been administrated. This results a higher surfactant protein pool and justifies the lower peak inspiratory pressure (PIP) required and the trend toward a better dynamic and static compliance and ventilation efficiency index (VEI). To conclude, these findings from this animal study demonstrate that even though these two synthetic corticoids have similar pharmacological properties, they still show different effects on the biochemical maturation of the fetal lung (Schmidt et al., 2017).

6.1.10. DOSE AND ROUTE AND RELATED ISSUES

The doses nowadays used are actually still the same as defined by Liggins (1972). 12 mg of betamethasone should be administrated intra muscularly in a 24 hours interval for women with imminent preterm birth before 34 + 0 weeks of pregnancy. Alternatively, 4 x 6 mg dexamethasone every twelve hours can be used (Leitlinienprogramm DGGG OEGGG SGGG, 2020). Commonly, 12 mg of a combination of betamethasone disodium phosphate and betamethasone acetate (1:1) has been injected twice within 24 hours in the muscle of the mother. In Austria this medication is known under the trade name Celestan biphase. Since 1995, this regimen is recommended by the National Institutes of Health (NIH) Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes (NIH 1995). However, it seems necessary to improve these regiment in order to avoid excessive fetal exposure to ACS and therefore limit potential side effects. It has been supposed that the dose applied may be higher than necessary (Jobe & Soll, 2004). Optimizing the dosage is therefore relevant, as increased exposure of corticosteroids for the fetus may lead to potentiate side effects.

In order to optimize the dosage of antenatal corticoids, recent animal studies aimed to compare dosing of different formulation of ACS inducing lung maturation. Regarding the influence of the dosage of betamethasone phosphate alone, it has been concluded that in case of reducing the dosage of betamethasone, a single dose 0.5 or 0.25 mg/kg of betamethasone did not influence fetal lung maturation. A lower dose improved dynamic and static lung compliance. The expression of surfactant has not changed after reducing the dosage. This arouses the suspicion that structural lung maturation may be more relevant in inducing lung maturation rather than biochemical changes in surfactant production (Schmidt et al., 2017). An animal study compared different glucocorticoid formulations in order to identify which prodrug improved the most the fetal outcome. A combination of betamethasone-acetate and betamethasone-phosphate has been compared to betamethasone-acetate, betamethasone-phosphate and dexamethasone-phosphate. The first intramuscular administration was at 122 ± 1 day of gestation. In pregnant sheep, when a 0.17 mg/kg dose of the combination of the two betamethasone prodrugs have been administrated intramuscularly, a fetal plasma peak of 12 ng/ml at 3 - 4h, which is tracible up to 12 hours, has been detected (Schwab et al., 2006).

According the collected data, the combination of betamethasone-phosphate + betamethasone-acetate was superior to dexamethasone-phosphate or betamethasone-phosphate alone regarding the promotion of biochemical and mechanical fetal lung maturation. A lower peak inspiratory pressure (PIP) requirement, an improved compliance and an increase in surfactant expression has only been found when betamethasone-phosphate + betamethasone-acetate has been administrated. Therefore, this combination has been favorized over the prodrugs. After injecting 0.5 mg/kg of the short acting steroids, dexamethasone-phosphate or betamethasone-phosphate, a higher fetal blood level has been found which showed no physiological benefits. No improvement of surfactant mRNA expression neither of the lung compliance have been reported. It has been concluded that rather lower and prolonged fetal exposure to corticosteroids, then higher peaks and shorter exposure influenced the improvement of fetal lung maturation. Thereby, the fetus is less exposed to corticosteroids and possible side effect might be avoided. These findings seem to be useful not only to distinguish the influence from the different prodrugs on the lung maturation but also to define the optimal corticosteroid exposure in human in order to improve fetal outcomes. Nevertheless, the optimal dose remains unexplored. It has been demonstrated that either a low-dose maternal infusion with betamethasone-phosphate for 36 hours or a single dose of the combination betamethasone phosphate and betamethasone acetate induce lung maturation. The effect persists until 48 hours and the efficacy was lost by 4 days (Schmidt et al., 2017).

In sheep model, it has been found that a dose of 0.125 mg/kg betamethasone-acetate component of the clinical drug and also a constant infusion of betamethasone phosphate induce lung maturation 48 hours after the treatment. Betamethasone level above 1 ng/ mL for 24 hours is required in order to induce lung maturation. Additionally, the importance of the lower dosage has been underlined by showing that much higher doses in shorter interval have not been efficient (Kemp et al., 2018). Increasing the dose did not influence the effectiveness of the lung maturation, in contrary it may lead to an increase risk of toxicity.

The issue mainly is that fetuses are exposed to unnecessary high concentrations of ACS for the desired maturation effect (Waljee et al., 2017). The aim of the treatment is therefore to reduce fetal exposure in order to prevent long term adverse effects. A 0.25 mg/kg i.m. single dose of betamethasone-acetate results both a low maternal and fetal betamethasone levels. When the dose of betamethasone acetate has been doubled, this prodrug was still as effective as the 1:1 mixture,

which is clinically commonly used. A significant increase in mRNA of surfactant proteins highlight the improvement in compliance. Clinically, this regimen shows potential benefits due to a lower maternal exposure of betamethasone and as a consequence also to a lower fetal exposure (Jobe et al., 2009).

Neither the choice of the drug nor the treatment schedule has been optimized even though there are still concerns about the excessive fetal exposure of corticosteroids which may be harmful. It is therefore necessary to find an adequate dosing in order to insure in one hand the lung maturation and in another hand to limit the potential risks (Jobe & Goldenberg, 2018; Kemp et al., 2018).

In has been proven in fetal sheep and monkey, that a single dose of betamethasone-acetate, which lead to a prolongated and lower exposure of corticosteroids may be equivalent to the clinical treatment, betamethasone-acetate and betamethasone-phosphate.

In order to ensure a constant exposure of ACS of the fetus, a maternal infusion also is possible. Even though lung maturation has been proven when this route has been applied, it still is inconvenient in low resource environment where oral administration is preferred because of being un-expensive and easier available. It seems therefore necessary to investigate the effectiveness and safety of oral treatment, which can be considered as a relevant alternative. Schmidt et al. recently investigated the oral corticosteroid treatment in rhesus macaque in order to demonstrate the effectiveness of the oral use. Betamethasone-phosphate and dexamethasone-phosphate which are given orally have been compared to the combination betamethasone-acetate and betamethasone-phosphate, which was considered as the positive control. The negative control group was exposed to saline. Also, results of the orally administrate prodrugs have been compared to data from non-pregnant monkeys. Fetal plasma concentration of betamethasone after intramuscular treatment of the prodrug betamethasone-acetate is 1 ng/ml and constant over 24 hours. Maternal plasma concentration in turn is about 2.5 ng/ml and therefore the fetal to mother ratio is 0.42. After dexamethasone-phosphate has been orally taken, the maternal plasma concentration is 10.4 ng/ml at 6 hours and at 24 hours 0.7 ± 0.4 ng/ml. The maternal half-life is 4.8 hours which is similar to the fetal half-life (4.3 hours). However, this results that fetal dexamethasone level is below 1 ng/ml by 24 hours. In case of an oral administration of betamethasone-acetate, fetal plasma level was in turn higher, namely 1.5 ng/ml and the fetal to maternal ratio was 0.49. These results may be associated with the lower clearance of this prodrug and may therefore lead to a longer exposure of

betamethasone. Another reason why a higher level has been noted is, that the half-life of betamethasone-phosphate is significantly higher, namely 7.4 hours compared to dexamethasone-phosphate. Previous findings underlined that plasma betamethasone level have to be maintained in a range of 1 - 4 ng/ml for at least 24 hours in order to induce lung maturation in sheep (Kemp et al., 2018).

Besides, the blood level of the two prodrugs after oral use were lower in maternal plasma compared to non-pregnant monkeys. It has been found that maternal cortisol was suppressed at 5 days only in case of the administration of the combination of betamethasone-acetate and betamethasone-phosphate. Tan et al. demonstrated that an increase of mRNA occurred shortly after fetal exposure to ACS in sheep models (Tan et al., 1999).

According to the data of RNA sequencing in the study published by Schmidt et al., specific effects of corticosteroids on different organs have been showed (Schmidt et al., 2017). Oral betamethasone-phosphate administration results in induction of genes involved in the biological process of cellular division in lungs but has a suppressive effect on genes associated with developmental process and differentiation. Betamethasone-phosphate induces genes involved in myeloid cell differentiation in the liver and suppressed genes related to morphogenesis and angiogenesis. There were on altered genes expressions in the hippocampus in case of oral administration.

After oral administration, higher initial plasma levels are reached faster compared to the intramuscularly administration of betamethasone-acetate. According to a shorter clearance of betamethasone-phosphate compared to dexamethasone-phosphate, the firstly mentioned drug persists longer in the body and therefore a less frequent dosage is required in case of re-treatment in order to keep steroids level above 1ng/ml in the plasma. Oral betamethasone-phosphate is therefore favorized regarding the compliance. There has been concerns about too high fetal exposure which may induce toxic effects. Even tough, higher doses of dexamethasone have been used in oral administration compared to intramuscular, no increased toxicity have been noted (Kemp et al., 2018). Peak concentration of maternal oral dexamethasone has been recorded at 3 hours whereas it is already reached at 30 minutes in case of an intramuscular administration.

According to the bioavailability, maternal oral dexamethasone represents 65% of the intramuscular level (Egerman et al., 1998).

The combination of betamethasone-acetate and betamethasone-phosphate is the most improving treatment. Regarding the route of application, dexamethasone can either be intramuscularly or orally administrated. According to Brownfood 2013, a significant increase of the incidence of neonatal sepsis has been reported when dexamethasone has been taken orally sepsis (RR 8.48, 95% CI 1.11 to 64.93). Intramuscular route is to favorize over the oral one.
However, the pharmacokinetics are still not been systematically evaluated to establish optimal drug choice, dose and treatments (Kemp et al., 2020).

6.1.11. BENEFITS OF THE SINGLE COURSE OF ACS

The following paragraph discusses the predominant advantages of ACS administrated in women at risk of imminent preterm birth. Liggins and Howie recognized the potential of this therapeutic option already in 1972. The findings were fundamental for further research in this field. He conducted a randomized controlled trial in order to investigate the effects of potent corticosteroids, having the ability to pass through the membrane and therefore reaches the fetal circulation. 117 mothers out of 282, who expected to deliver prematurely before 37 weeks of pregnancy, were exposed to betamethasone. The administration of the drug induced an acceleration of the fetal lung's functional and morphological maturation occurring within 48 hours. The incidence of RDS which is considered as the leading cause of death in preterm infants, has been notably reduced when betamethasone was administrated before birth. Actually, the difference in incidence of RDS between infants who were delivered less than 24 hours was already significant (9% in betamethasone group compared with 25.8% in controls). Though, when birth occurred after the time, the incidence of RDS was 4.3% in infants exposed to the corticosteroid whereas the incidence of RDS was 6-fold higher in the control group. These findings underlined the beneficial effect of antenatal corticosteroids that was even more marked 24 hours after the exposure. IVH was found in 5.3% of the control infants, but in none of the treated infants. Therefore, Liggins and Howie (1972) indicated the influence of betamethasone in preventing IVH. An additional advantage of this treatment was that no complications of pregnancy, labor, delivery or puerperium have been reported and this therapy did not lead to a higher risk of fetal or neonatal infection. Lastly, related to the betamethasone exposure a significant lower perinatal (6.4 % of the treated group compared to 18.0% of the control group) and early neonatal death rate (3.2% of the treated compared to 15.0% of the controls) have been found.

According to the first study evaluating the ACS treatment in human, it has been concluded that the antenatal administration of this drug was certainly beneficial in improving the outcome of preterm infants. Those were only the preliminary findings regarding the therapy's advantages of the first study in human.

Now the focus is on the updated and supplementary results of the Cochrane Review. The treatment of ACS leads to an improvement of neonatal outcome. This has been underscored by a significant decrease of RDS. According to the data of the Cochrane Review conducted by Roberts et al. (2017) in which 30 studies have been revised (7774 women and 8158 infants), the average risk ratio of RDS was 0.66 with an 95% confidence interval of 0.56 to 0.77 taking under consideration that this has been calculated from 7764 participants of in total 28 studies. These results are in favor of the use of corticosteroids and simply highlight that the occurrence of RDS is significantly less likely found when corticosteroids have been administrated. A reduction in moderate and severe RDS has as well been proven and the average risk ratio was 0.59, 95% with a confidence interval of 0.38 to 0.9 (in 6 studies inclundinf 1686 participants).

To conclude, an average reduction of 34% in RDS and a reduction of 41% in moderate to severe RDS have been associated to the administration of ACS. However, the influence on chronic lung disease remained uncertain.

Likewise, IVH is considered as a serious complication and is associated with significant morbidity. According the data from 6093 participants of in total 6 studies the average risk ratio for IVH is 0.55 with an 95% confidence interval of CI 0.40 to 0.76. This result highlighted once again that corticosteroids use may beneficial in reducing the incidence of this complication. An overall reduction in IVH of 47% has been demonstrated. Also, a significant reduction of NEC has been underlined when corticosteroids have been used (RR 0.50, 95% CI 0.32 to 0.78). These finding result from 10 studies including 4702 participants. According to the data of 1753 subjects of eight studies, a marked reduction of systemic infections occurring in the first 48 hours of life have been proven (RR 0.60, 95% CI 0.41 to 0.88) (Roberts et al., 2017).

More importantly, perinatal or neonatal death have been reduced notably which underlines once again the relevance of the antenatal treatment with corticosteroids. Average risk ratios are respectively 0.72 with a 95% confidence interval (CI) 0.58 to 0.89 when 6729 participants from 15 are included and 0.69, with a 95% confidence interval of 0.59 to 0.81 resulting from 7188 participants of 22 studies. This resulted an overall reduction of perinatal death of 28% and neonatal

death of 31% with exposure of corticosteroids. This Cochrane Review of 2017 highlighted once again the importance of the use of ACS by demonstrating that the treatment is associated with a notable reduction in the most serious complications related to preterm birth.

A significant lower rate of the composite outcomes of severe respiratory complications has been associated with the ACS administration. The number needed to treat to prevent one case was 25 (95% CI, 16 to 56). All in all, the rate of transient tachypnea of the newborn (6.7% vs. 9.9%), bronchopulmonary dysplasia (0.1% vs. 0.6%), as well apnea (13.9% vs. 17.8%) were significantly lower after betamethasone exposure (Gyamfi-Bannerman et al., 2016).

Less respiratory support was required in neonates which were exposed to corticosteroids before birth. For instance, a reduction in the need for mechanical ventilation / CPAP (RR 0.68, 95% CI 0.56 to 0.84) has been noted in 3556 neonates from 6 different trials. Due to the prenatal administration of corticosteroids the need of surfactant of the infants was also reduced (RR 0.68, 95% CI 0.51 to 0.90). These finding results from 5 studies including 3556 participants (Roberts et al., 2017.Due to the use of antenatal corticosteroids, fewer infants had an Apgar score less than 7 at 5 minutes of age (RR 0.81, 95% CI 0.67 to 0.98. This results from 10 studies including 2419 participants. Resulting from this the infant is in good health conditions and as a consequence they are less likely to be admitted into a Neonatal Intensive Care Unit (NICU) (RR 0.90, 95% CI 0.84 to 0.97; according 7 studies including 3803 participants. Further, unexposed infants spent more commonly 3 or more days in the intensive or intermediate care nursery. Concerning the mechanical support, it has been ascertained that the time requiring mechanical ventilation was independent of the corticosteroid use. There are additional similar findings in the group exposed to corticosteroids and the placebo group regarding several outcomes such as air leak syndrome (RR 0.76, 95% CI 0.32 to 1.80; participants = 2965; studies = 2) or the incidence of small-for-gestational-age infants (RR 1.11, 95% CI 0.96 to 1.28; participants = 3478; studies = 5). A comparable interval between trial entry and delivery has been reported between the two groups (MD 0.23 days, 95% CI -1.86 to 2.32 days; participants = 1513; studies = 3) (Roberts et al., 2017).

ACS may support neonatal adaptation including improvement of the kidney function or better metabolic transition. As well, an improved cardiovascular adaptation has been reported (Hillman et al., 2012). It has been demonstrated that ACS use leaded to less need for blood pressure support during the first 48 hours postpartum in extremely premature infants (Moise et al., 1995). Further,

an improvement in neuroendocrine and endocrine responses to postdelivery hypoxic challenge was seen after ACS administration (Ervin et al., 2000).

The treatment with corticosteroids leads to a significant reduction of the incidence of severe complications including RDS, IVH and NEC. Likewise, the risk of perinatal death and neonatal death are reduced. Therefore, the short-term beneficial effect of a single treatment course in women at risk of imminent preterm birth grossly outweighs the potential risks.

Antenatal corticosteroids in fetal growth restriction

There is a lack of data from randomized trials on benefits and risks of an ACS exposure aiming to improve the outcomes in fetuses with intrauterine growth restriction (Magann et al., 2017). However, a large study of intrauterine growth restriction (IUGR) fetuses demonstrated that the risk of RDS of overall IVH and of severe IVH have significantly decreased after antenatal corticosteroids exposure (Bernstein et al., 2000). Schaap et al conducted a case-control study including infants with growth restriction and born preterm at 26-32 weeks of gestation. A control group consisting 62 infants have been compared to the same number of infants, which in turn were exposed to antenatal corticosteroids. The marked outcome was that survival was associated with no disability or handicap at 2 years' corrected age. In a long-term follow-up, no differences in behavior has been reported (Schaap et al., 2001).

It has been concluded that benefits from the treatment may outweigh possible adverse effects.

Benefits in childhood

According to the Cochrane review, less developmental delay has been found in childhood (RR 0.49, 95% CI 0.24 to 1.00), more precisely at 3 years follow-up. For evaluating continuous data, mean difference (MD) has been used with 95% confidence interval where the same instrument was used to measure outcomes. Considering the outcome of two studies, no differences were seen in childhood weight (MD 0.30 kg, 95% CI -0.39 to 1.00 kg, participants = 333), in height (MD 1.02 cm, 95% CI -0.26 to 2.29 cm; participants = 334) and in head circumference (MD 0.27 cm, 95% CI -0.08 to 0.63 cm; participants = 328) (Roberts et al., 2017).

Furthermore, no adverse events on postnatal lung function have been remarked. Similar results were found regarding vital capacity (VC) and forced expiratory volume in one second (FEV1) between children with and without ACS treatment. It has been suggested that lung function has not been altered in childhood when corticosteroids have been used in order to improve primary neonatal outcome. Systolic blood pressure has also not altered significantly (MD -1.60 mmHg, 95% CI -4.06 to 0.86 mmHg; participants = 223). Similar results were found for children with and without ACS administration regarding visual impairment and hearing impairment. Likewise, behavioral, learning difficulties and intellectual impairment were not observed more frequently when corticosteroids have been used (Roberts et al., 2017).

All in all, the antenatal treatment seems to be safe for women in high-income countries. Nevertheless it has been concluded that there were no beneficial effects regarding chronic lung disease and death in childhood or death into adulthood (Roberts et al., 2017).

Maternal benefits

According to the data collected of the Cochrane review, maternal benefits have also been noticed which may support the use of antenatal corticosteroids. This treatment did not lead to an increased risk of maternal infection such as chorioamnionitis (RR 0.83, 95% CI 0.66 to 1.06; in 10 studies including 5546 participants) and endometritis (RR 1.20, 95% CI 0.87 to 1.63 resulting from 10 studies including 4030 participants) (Roberts et al. 2017). This truly speaks for the therapy, as infection may induce premature birth and is also the main source of maternal morbidity (Mercer, 2003). The risk of maternal death was also not increased after corticosteroid exposure. Even if ACS have been administrated in complicated settings such as severe preeclampsia or HELLP no differences in maternal death between treatment and control group has been reported (Magann et al., 1993). No adverse effects on the disease process have been reported. It is generally accepted that short administration of high-dose corticosteroids is effective in improving maternal platelet count and liver function, and this has been recommended as a therapeutic route for patients with HELLP syndrome with severe thrombocytopenia (Isler et al., 2001; Tompkins & Thiagarajah, 1999) .

As a conclusion, no statistically significant differences between the control group and the exposed group were evident regarding perinatal morbidity after corticosteroid treatment. So, even in

pregnant women with HELLP syndrome, the therapy may be justified because same positive outcomes such as less neonatal RDS have been noted compared to patients without HELLP syndrome.

Antenatal Corticosteroids in PPROM

Magann et al (2017) reviewed 17 controlled trials, in which more than 1900 pregnant women complicated by PPROM and exposed to ACS have been compared to women who did not receive corticosteroids. According to the findings, the treatment leads to a reduction of perinatal risks such as IVH grade III and IV RR 0.49, (95% CI 0.25-0.96), IVH grade I-IV (RR 0.52, 95% CI 0.37-0.72) and RDS (RR 0.82, 95%CI 0.67-0.98). Additionally, similar outcomes for the corticosteroids exposed group and the control group concerning the risk of NEC and neonatal sepsis have been found. Furthermore, comparable Apgar score at 5 minutes has been noted. According to this meta-analysis, it has been demonstrated that mortality and morbidity have been reduced after ACS treatment (Been et al., 2011). ACS are not leading to an increased risk of maternal and neonatal infection. However, in severe cases of an amnion infection syndrome delivery has to take place even before lung maturation has been achieved (less than 24h after beginning of treatment).

6.1.12. RISKS ASSOCIATED WITH A SINGLE COURSE OF ACS

Short-term effects

Nevertheless, the antenatal treatment with betamethasone is also associated with potential risks.

A reduction in the amniotic fluid volume, decreased fetal breathing and as well decreased fetal movement count to the short-term effects of corticosteroids administered (Jackson et al., 2003).

Further, a small decrement of the birthweight between 26-34 weeks of gestation has been reported (Bloom et al., 2001). This short-term adverse effect is however more significant when multiple courses have been administrated (Banks et al., 1999). As well, the treatment of antenatal corticosteroids may alter the weight of several organs such as liver, lungs, hear, thymus and kidney.

Growth restriction

Growth restriction was also a short-term effect of corticosteroids, which occurred actually more frequently in infants exposed to multiple courses of corticosteroids and is therefore a minor effect related to a single course. It has been demonstrated that infants administrated with corticosteroids were lighter compared to unexposed ones but clarified that this change did not persist into childhood or even adulthood (Braun et al., 2015). Growth restriction is an adverse effect only occurring in the very early life and is only a matter of concern in the event of multiple administrations. Fetal growth restriction is closely associated not only with increased bronchopulmonary dysplasia but also with infant mortality and may also influence the development of the nervous system (Murray et al., 2015).

Nevertheless, the World Health Organization (WHO) highlighted that physical growth beneath the 10th percentile appears more likely when antenatal corticosteroids have been exposed (OR 5.20, 95% CI 1.38–19.6).

All in all, these effects are actually more frequently seen in case of multiple steroid courses.

Cardiovascular adverse effects

The gestational age has an impact on the responsiveness of betamethasone. A decrease in fetal heart rate on day one, a reduced breathing activity and prolonged episodes of quiescence with a concomitant decrease in body movements on days 1 and 2 for fetuses exposed to the synthetic corticosteroid at 29-34 weeks of gestation has been noted (Mulder et al., 2004). These changes were not noticed between 26 and 28 weeks of gestation. Presumably ontogenetic changes in these mechanisms are fundamental.

It seems therefore important to assure an adequate monitoring of the blood pressure and glucose availability after preterm birth.

Hypoglycemia

One of the outstanding adverse effect of the ACS treatment is certainly the hypoglycemia in the newborn. This is especially in low-resource environment a substantial issue. In high resource

environment is can easily be managed due to a great medical care and diagnostic tools. Hypoglycemia is found when the serum blood glucose is below 45 g/dL. According to Gyamfi-Bannerman et al. (2016), neonatal hypoglycemia was commonly shown in fetuses whose mother was exposed to betamethasone during pregnancy compared to those whose mother was exposed to placebo (24.0% vs. 15.0%; Risk Ratio, 1.60;95% CI, 1.37-1.87; P<0.001). In fact, the greater risk of hypoglycemia is particularly in late preterm pregnancies and is one of the most common complications. As a consequence, to a lower glucose level, poor cognitive and motor function at 4.5 years of age has been found (McKinlay, Cutfield, et al., 2017).

Barker hypothesized that excess exposure of antenatal corticosteroids may contribute to in fetal programming of chronic disease. In order to adapt to a restricted availability of nutrients, the fetus permanently change their metabolism. A decrease of anabolic hormones including insulin and insulin-like growth factor and an increase in catabolic hormones such as glucocorticoids has been noted. These 'programmed' changes could underlie the development of diseases in later life, such as insulin resistance, coronary heart disease and the related disorders stroke, diabetes and hypertension (Barker DJP, 1998). Benediktsson et al. illustrated the impact of antenatal corticosteroids on the fetal origins of adult disease hypothesis. According to his findings of an animal study, lower birthweight and higher blood pressure were reported in adult rats whose mother was exposed to corticosteroid during pregnancy compared to offspring of control rats. Moreover, an increased fetal exposure of maternal glucocorticoids may be associated to low birthweight and large placenta. This outcomes in turn significantly predict hypertension (Benediktsson et al., 1993).

A recent study confirmed once again that hypoglycemia was associated with corticosteroids treatment before birth in order to prevent RDS. There are still several hypotheses to the origin of this complication. In fact, ACS administration causes maternal hyperglycemia which in turn leads to a hyperplasia of fetal pancreatic beta cells. Fetal and also neonatal hyperinsulinemia results (Pettit et al., 2014).

Actually, lower birthweight correlates with the occurrence of hypoglycemia could be one of the strongest risk factor. This adverse effect has been found in early and late preterm infants. Besides, fetal growth restriction may also be considered as a risk factor. However, it remains challenging to quantify the net contribution of maternal steroids on the occurrence of neonatal hypoglycemia due to a lack of control group in this study. It seems therefore necessary to carry out glucose monitoring

when antenatal corticosteroids have been administrated before even symptoms occur (di Pasquo et al., 2020).

Long-term effects

Insulin resistance

The treatment of corticosteroid before birth may also have long-term metabolic effects. In adulthood, altered glucose metabolism has been reported for those individuals antenatally exposed to antenatal corticosteroids (Kelly et al., 2012). In a follow-up study cardiovascular risk factor in individual with ACS treatment have been examined and no differences in growth, blood lipids or cortisol have been noticed. But an increase plasma insulin concentration at 30 min following a fasting 75 g oral glucose tolerance test was found for participant exposed to antenatal betamethasone (mean difference is 0.16 log insulin units, 95% CI 0.04 to 0.28 log insulin units; in 412 participants). After 120 minutes, a reduction in glucose concentration has been noted (mean difference is -0.27 mmol/L; 95% CI -0.52 to -0.02 mmol/L; in 410 participants). These changes may be associated to the administration of ACS (Liggins and Howie 1972). So, it has been concluded that the antenatal corticosteroids treatment may lead to an insulin resistance in adult offspring (Dalziel et al., 2006). A transient elevation of insulin and c-peptide were detected in cord blood. Homeostatic Model Assessment of Insulin Resistance Index (HOMA-IR) was as well elevated which is indicative for insulin resistance (Verhaeghe et al., 2005).

In animal experience, increased blood pressure has been observed in adult animals exposed to ACS in addition to the impaired glucose tolerance (Clark, 1998; Dodic et al., 1999; Edwards et al., 2001). An increased diastolic and systolic blood pressure have been identified in 14-year-old participants exposed to betamethasone antenatally. However, these data could not be fully valid due to the large influence of puberty on the blood pressure (Doyle et al., 2000). But a decrease of aortic distensibility have been shown in adults at 23-28 years of age who were treated with corticosteroids before birth and born with an average birthweight of 1.2 kg compared to the controls. Therefore, future cardiovascular diseases cannot be excluded (Kelly et al., 2012).

„Thus, while the finding of increased insulin resistance in adulthood provides support for excess corticosteroids as a mechanism underlying the fetal origins of adult disease hypothesis, it should

not be seen as a reason to withhold antenatal corticosteroids given the large and clinically substantial benefits seen in the neonatal period" (cited from Roberts et al., 2017).

Renal adverse effects

In animal studies a reduction in glomerular numbers and function after maternal glucocorticoid treatment has been pointed out (Martins et al. 2003).

A multicenter, prospective and follow-up study aimed to assess new finding regarding long-term metabolic risks, including renal function, of a single maternal betamethasone course in adolescence. The 412 subjects were born before the 32th week of gestation with a very low birthweight, namely below 1 500 g. The study was focused on body composition like insulin resistance and renal function. The only adverse effect found was a lower glomerulus filtration rate at 19 years of age. The GFR was 25.2 ml/min with an 95% CI 28.9 to 21.4 per 1.73 m^2, so a reduction of -5.2 ml/min with 95% CI, -8.9 to -1.4 per 1.73 m^2 (Finken et al., 2008). Actually, this change is not clinically relevant, but it might be supportive in predicting an increased risk of chronic renal failure in adolescent prematurely born and exposed to antenatal corticosteroids at 32 weeks of gestation.

The accelerated maturation of the kidney due to corticosteroid exposure may be beneficial but in later life a decreased function of the kidney has been reported in a cohort study. Adolescents born prematurely whose mothers were exposed to corticosteroids had abnormal renin angiotensin system function compared to a preterm cohort whose mothers were not exposed to antenatal corticosteroids. This may lead to an increased risk of renal inflammation and fibrosis and lastly hypertension and renal disease (South et al., 2017).

Cerebral adverse effects

Initially, findings from animal studies demonstrated the impact of a single course of antenatal corticosteroids on the brain and found a decrease of brain growth (Amorim et al., 1999). These findings have been confirmed in animal studies conducted by Huang 1999 and Jobe 1998. Thus, there is concern about long-term neurodevelopment after antenatal exposure. According to the Cochrane review 2017, no differences in neither intellectual impairment nor educational achievement between those exposed to a single course of antenatal corticosteroids and those

exposed to placebo have been reported in follow-ups into adulthood. These findings evoke the previously presumed influence of corticosteroids on neurodevelopment.

There still were concerns about the potential side effects in the brain such as inducing early maturation or programming effects. In fetal monkey, morphologic hippocampal injury has been found related to maternal dexamethasone treatment (Uno et al., 1990). Also, alteration of hippocampal mRNA expression and DNA methylation has been observed into the third generation in guinea pigs (Crudo et al., 2013).

It also has been showed that there were long-lasting effects of ACS exposure on hypothalamic-pituitary-adrenal reactivity in term-born children which have implications regarding the vulnerability for health and mental disorders (Alexander et al., 2012).

The development of the fetal Hypothalamic-Pituitary-Adrenal (HPA) axis is influenced by of endogenous and exogenous such as synthetic glucocorticoids during pregnancy. Programming of long-term effects can therefore result. An abnormal increased level of glucocorticoid may influence stress responsive systems. According to the assessments of cord blood and amniotic fluid, an increased bioactivity of glucocorticoid has been detected (Kajantie et al., 2004). Synthetic glucocorticoids lead to an acute suppression of endogenous fetal cortisol production which seems to persist into the immediate postnatal period (Marinoni et al., 2008). More precisely, suppression of cortisol level remains until the first postnatal week and afterwards returns to basal levels (Nykänen et al., 2007). A single antenatal course of betamethasone lead to a suppression of the cortisol response to the painful stress of a heel-stick blood draw among preterm infants. New findings demonstrated also that this effect actually remains up to 6 weeks after birth. Exposure to multiple corticosteroid courses may have a greater impact on the regulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis (Waffarn & Davis, 2012). The suppression of basal level of cortisol was only found during the first several days whereas the impact on Hypothalamic-Pituitary-Adrenal (HPA) axis persists (P. L. Ballard et al., 1975).

There are concerns that altered Hypothalamic-Pituitary-Adrenal (HPA) axis during infancy may be significant for physiological and behavioral problems in later life (Philips DI, 2007). There was a difference between betamethasone and dexamethasone in the outcome associated with the neurobehavioral development in mice. It has been shown that betamethasone is preferably used because dexamethasone caused a development delay and altered neurobehavioral performance compared to the drug of choice (Rayburn et al., 1997).

It is known that, an increased cortisol level in the newborn is a typical response to stress and is related to longer sensitization to pain and stress even in childhood (Duerden et al., 2018).

In a recent study published by McKindley, it has been shown that an antenatal exposure of corticosteroids may lead to an increased risk of poor cognitive function and visual motor function at 4 years of age in children who had neonatal hypoglycemia (McKinlay, Alsweiler, et al., 2017).

Premature birth remains a major contribution to adverse outcomes. The importance of threatened preterm labor on altering outcomes has been highlighted in a recent study (Paules et al., 2017). To give a further example, an average lower IQ and altered motor function has been detected in preterm infants compared to those born at term. It has been supposed that preterm infants may be less resilient to stress and injury (Johnson & Marlow, 2017).

psychological adverse effects

Adults who have been prenatally exposed to corticosteroids had significantly more psychopathology which can be associated to the treatment (Savoy et al., 2016).

Further potential adverse effects of glucocorticoids (Fachinformation, Celestan biphase)

Prolonged therapy with glucocorticoids leads to a pronounced inhibition of endogenous production and release of CRH and ACTH, depending on the dose and duration of therapy. As a result, the formation of endogenous glucocorticoids is greatly reduced or completely eliminated. If the exogenous glucocorticoid supply is stopped too quickly, it can lead to clinically apparent adrenal cortical insufficiency, since the physiological regulation of glucocorticoid formation only restarts after a certain delay. The glucocorticoid withdrawal syndrome which then occurs is characterized by fever, myalgia, arthralgia and general weakness. A main issue seems very difficult to distinguish these symptoms from a resurgence of the underlying disease treated by the glucocorticoids. This is the reason why glucocorticoids therapy should not be last longer than one week and should not be terminated too early. Due to the immunosuppressive, antiphlogistic and antiproliferative effect, the risk of infection is increased and a disturbance in wound healing is noticed under glucocorticoid

therapy. Myopathy usually occurs due to the katabolic mechanism of action of glucocorticoids. Long systematic therapy may be accompanied by several complications such as cataract, glaucoma, depression, euphoria, acne, hypertrichoses or even telangiectasia. In too high concentration symptoms of Cushing syndrome occurs like hypertonia, weakness, fatigue, amenorrhea, changes in fat distribution. A reduction in glucose tolerance under glucocorticoid administration can lead to the development of manifest diabetes mellitus.

6.1.13. REPEATING THE COURSES

6.1.13.1. RESCUE COURSE

In the initial trials concerning the use of antenatal corticosteroids, Liggins and Howie (1972) noticed that the beneficial effects diminish 7 days after administration. Therefore, a repeated course should be taken under consideration in case of a persistent risk of imminent preterm birth. The question now is, how exactly to proceed, if after the first treatment with corticosteroids the pregnancy still continues, knowing that 50% of women remain pregnant for 7 to 14 days after steroids treatment(Bonanno & Wapner, 2012).

The first administration of antenatal corticosteroids is beneficial due to a decrease of RDS of around 35%. In 2000, repeat treatment was evaluated at a second NIH-sponsored consensus conference and it was agreed that repeated treatment should be given once at a precise interval of 7 to 14 days after the first administration. The reason was the worrying increase of RDS in deliveries beyond 7 days (Jobe & Goldenberg, 2018). It has been recommended to repeat the course 7 day after the initial for women in case of a greater risk of imminent preterm birth. The use was limited for gestational age less then 29 + 0 (Leitlinienprogamm DGGG OEGGG SGGG, 2020). Additionally, according to ACOG 2012a, a single antenatal betamethasone course, rescue dose, has been recommended 7 to 14 days after initial course in case of an increased risk of imminent birth before 33 weeks´ gestation. These recommendations have further been confirmed worldwide (WHO, 2015).

Timing is very influencing in terms of improving the treatment and remains critical particularly for mothers with a high risk of immediate preterm delivery. One study showed that the effect is

suboptimal when ACS have been given 24 hours before delivery. It has been found that a single use of ACS after 24 hours before preterm birth lead to a decrease of RDS and seems therefore efficient for infants born between 28-34 gestational weeks (Peltoniemi et al., 2007; Vermillion et al., 2001). The use of the lowest dose required for an efficient effect, can also contribute to an improvement and thus minimize potential dose-dependent risks (Reynolds, 2013). An improvement of this "rescue course" has been confirmed following the finding in different trials. A "rescue course" before 33 weeks improved neonatal outcome. Compared to placebo, a second course lead to a significant decrease in RDS, ventilation support and surfactant use. It can therefore be considered that respiratory compliance has been improved after a single repetition of the course. Furthermore, neonatal morbidity was reduced (43.9% vs. 63.6%) (Garite et al., 2009). A reduction of morbidity and mortality has been reported in a study concerning rescue steroids following the initial course administrated at less than 34 weeks of gestation. Neither birthweight nor head circumference has been influenced (McEvoy et al., 2010).

Furthermore, a second course of betamethasone showed both short-term and long-term benefits. According to a Cochrane review, a significant reduction of RDS risk has been found (RR = 0.83, 95% CI 0.75–0.91). Additionally, no evidence of significant damage after a 2-year follow-up has been found (McKinlay et al., 2012). In a follow-up study, no difference in growth or neurological development during early childhood has been reported after a "rescue course" (Peltoniemi et al., 2009). These findings support the administration of a single repeated course.

6.1.13.2. REPEATED MULTIPLE COURSES

It has been confirmed that a single repetition of corticosteroids is beneficial for women who are still at risk of imminent preterm birth. The issue is now to determine the frequency and the timing of the administrated courses.

Since 2000, repeating the courses of corticosteroids became more common in the United States, in United Kingdom and Australia but the potential risks and benefits remained unknown. Therefore, the Maternal-Fetal Medicine Units (MFMU) and Network of the National Institute of Child Health and Human Development (NICHD) investigated the use of repeated antenatal corticosteroids by comparing the outcomes of infants whose mothers repeating the courses with infants whose mothers belonged to the placebo group (Wapner et al., 2006). It was found that there was an

improvement in neonatal lung function by repeating the doses especially for those infants delivers before 32 weeks' gestation.

Optimal timing of repeating ACS courses is very challenging. In one Study, infants were exposed to repeated course less than 24 hours before birth whereas in two other studies 90% of the infants received it later (Garite et al., 2009; McEvoy et al., 2010; Peltoniemi et al., 2007).

An increased risk of severe RDS can be found when treatment with antenatal betamethasone has been repeated less than 24 hours before birth (Peltoniemi et al., 2007).

Risks and benefits associated with multiple ACS courses vary according the gestational age. Zephyrin and collaborators (2013) have investigated the balance between the advantages and disadvantages of repeated ACS application in neonates with risk of fetal growth restriction. The calculation was based on the results of the study of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal-Medicine-Units Network. It has been found that repeating the courses of ACS was less beneficial at advanced gestational weeks and therefore a repeated administration of ACS especially before 29 weeks seems adequate (Zephyrin et al., 2013). Repeating the course after 29 + 0 weeks of gestation was associated with increasing disadvantages for the children. Childre born after after 37 + 0 week of gestation, had a significantly higher rate of neurosensory developmental disorders (Elizabeth v. Asztalos et al., 2013). Before 29 + 0 weeks of gestation the treatment can be given to women to whom the first administration was more than 7 days ago and who are still at increased risk of preterm birth (WHO 2015). If it has been decided that the treatment of corticosteroids should be repeated, then the combination of betamethasone-phosphate and betamethasone-acetate is most commonly chosen (Brownfoot et al., 2013).

Neonatal outcomes

Not only a "rescue course" but also a weekly, biweekly repeated betamethasone lead to a significant decrease of RDS among preterm infants (Peltoniemi et al., 2011). In a Cochrane review, 10 trials have been reviewed in order to evaluate the impact of multiple courses of ACS in women remaining at risk of preterm birth. The most outstanding benefits were the reduction of the risk of RDS by 17% and the reduction of the risk of serious infant outcomes. Less supportive measurements such

as mechanical ventilation, surfactant use, oxygen supplementation or inotropic support treatment were required in infants exposed to multiple courses of corticosteroids. It has also been noted that the reduced risk of the patent ductus arteriosus were associated with this treatment. Less severe lung disease in the neonatal period occurred after repeated treatment (Crowther et al., 2015). These short-term benefits support the administration of multiple courses one week after the initial course in women remaining at risk of preterm birth.

Nevertheless, the multiple administration of ACS is also associated with potential risks. Multiple courses may influence intrauterine growth. Weekly or biweekly repeated betamethasone has been associated with restricted intrauterine growth (Peltoniemi et al., 2011). It has been found that mean birth weight, mean head circumference, head circumference Z scores and mean head length were reduced in infants exposed to repeated courses of antenatal corticosteroids ($p=0.001$, $p=0.001$ and $p<0.0001$, respectively). More precisely, the mean birthweight difference was -75.79 g, 95% CI -117.63 to -33.96, according to 9 trials, found in 5626 infants) but outcomes that adjusted birthweight for gestational age (birthweight z scores, birthweight multiple of the median and small for gestational age) did not differ between treatment groups. But differences for weight, head circumference and height were no more noticed by the time of discharge from hospital and also in latter childhood. Measures of body size are dependent on gestational age. Without any adjustment for gestational age it is not possible to fully assess the effects of repeated ACS treatment on fetal growth. This also was previously found in an animal study concerning fetal sheep exposed to multiple corticosteroid courses (Ikegami et al., 1997). Birth weight and head circumference decrease is associated with the number of courses. The importance of the frequency of the repeated courses is therefore underlined. These effects have only been noted when the courses have been repeated more than 2 times. Hence it has been considered that these effects are dose dependent (Hanna Norberg et al., 2011). Increased bronchopulmonary dysplasia, infant mortality and poor neurodevelopmental outcomes may also be related to infant fetal growth restriction (Murray et al., 2015).

In animal studies it has been reported that the number of glucocorticoid receptors in the brain was reduced after ACS use. Changes in fetal hypothalamic-pituitary adrenal development and function during postnatal life may be associated with this treatment. In sheep the impairment of the neuronal development was underlined by an altered retinal development, altered nerve growth, alter cerebral

maturation, a delayed rate of myelination and a decrease of the brain size (Antonow-Schlorke et al., 2009; Dunlop et al., 1997; Quinlivan et al., 2000). In animal studies, it has been found that multiple courses of antenatal corticosteroids may have deleterious effects on critical nerves within the central nervous system such as the optic and auditory nerve (Davis et al., 2009). Slower neural transmission times along the auditory nerve and brainstem auditory pathway and associated hearing deficits (Church et al., 2012). Disrupted retinal development was still visible days after multiple doses of antenatal corticosteroids. A thinning of the retina has been found and furthermore the myelination of the axons of the optic nervous system was significantly delayed (Dunlop et al., 1997; Quinlivan et al., 2000). Disturbed myelinization is of particular importance in early gestational age when myelination begins. Therefore, these effects could be considered to be age dependent. According to Antonow-Schlorke et al. (2009) "a single treatment was reported to have a transient effect on myelination, whereas repeated treatment was shown to result in persistent disturbance." Additionally, a decreased number of neurons and a dose dependent degeneration of neurons in the hippocampus was detected in studies in monkeys. According to these findings, it was therefore interesting to find out whether this change is also evident in humans.
A prolonged neonatal adrenal suppression may be associated with multiple corticosteroid exposure. Neonates receiving more than 3 courses had lower levels of plasma cortisol 2 hours after birth occurred. Moreover, they also had an increased risk of death (adjusted odds ratio 2.8%; 95% confidence interval, 1.3-5.9) (Banks et al., 1999).

In conclusion the repeated use of the mixture of betamethasone acetate and betamethasone phosphate has no benefits in reducing mortality and NEC (Jobe & Goldenberg, 2018). Compared to a single course of corticosteroids, repeating the courses may not reduce the incidence of IVH (Peltoniemi et al.,2011).

Based on these neonatal outcomes, the recommendation of repeating the use of antenatal corticosteroids should be selectively.

Childhood outcomes

According to a non-randomized regional cohort of singleton pregnancies followed up to 3 years, 3 or more courses of corticosteroids may lead to an increased rate of aggressive or destructive and hyperkinetic behavior (French et al., 2004).

Crowther et al. compared the different outcomes between 2-year-old antenatally exposed to placebo and those antenatally exposed to betamethasone. It has been pointed out that no differences in body size, blood pressure, use of health services, respiratory morbidity were found (Crowther et al., 2007). Concerns have been raised about long-term consequences on neurodevelopment after finding out that multiple courses of betamethasone may restrict intrauterine growth (Peltoniemi et al., 2011).

At two years of age, an increased amount of leukomalacia and neurodevelopmental abnormalities have been associated with a repeated administration of dexamethasone (Spinillo et al., 2004).
Follow-up studies of randomized trials involving either weekly or biweekly repeated courses or a single rescue dose of antenatal betamethasone did not reveal significant differences in neurological development or growth at the age of two years (E. v. Asztalos et al., 2011; Crowther et al., 2007) compared the two years outcomes of children exposed to multiple courses to those belonging to the placebo group. They found out that multiple courses may neither influence death nor neurological impairment at 18 to 24 months.
3 years later, the authors investigated the outcomes at 5 years in the Multiple courses of Antenatal Corticosteroids for Preterm Birth Study so called MACS-5. It is an international, multicenter, double-masked, randomized controlled trial. They aimed to evaluate any association between the gestational age at birth and the frequency of the courses used. The corticosteroids are given every 14 days until 33 weeks of gestation or birth to a single course in women at increased risk of preterm birth. In order to emphasize the importance of timing, the authors found out that the gestational age does have an influence in the treatment. They concluded that the risk of neurodevelopmental and neurosensory impairment by 5 years of age may be increased for children born after 37 weeks and exposed to multiple courses of ACS. The odds of neurosensory difficulties by 5 years of age may be significantly increased in children antenatally exposed to multiple courses and born at term. Practice of 3-4 courses is therefore not recommended. It seems necessary that the frequency of the administration has to be clearly defined (Asztalos et al., 2013). Multiple courses of corticosteroids

may reduce the risk of cerebral palsy (French et al., 2004). However, Wapner et al. (2007) recognized that especially 4 or more courses of antenatal betamethasone leads to a tendency towards increased cerebral palsy. There are therefore concerns that corticosteroids will significantly affect the development of nervous system. Cerebral palsy was found at 5 of 6 children exposed to 4 to 5 courses. Therefore, the possibility of a dose-response effect may be taking under consideration. They do not exclude neurologic consequences due to a repeated exposure. No differences in anthropometric measurements were found in the study even though more children in the repeat-treatment group had measurements below 10^{th} percentile (Wapner et al., 2007). In another study, which also exanimated children whose mothers participated in the Australasian Collaborative trial of Repeat Doses of Corticosteroids, authors focused on changes in neurodevelopment in mid-childhood. Both the saline placebo group and the group administered with betamethasone showed similar survival rates without neurosensory disability (78.3% repeat versus 77.3% placebo; risk ratio 1.00, 95% confidence interval, 0.94–1.08). It has been found that either the risk of neurodevelopmental or neurosensory impairment was increased mainly for 5-year-olds born after 37 week of gestation and antenatally exposed to multiple courses of corticosteroids.

Nevertheless preterm birth remains the primary cause for neurodevelopmental outcome regardless the number of course (Asztalos et al., 2014).

Concerns about the use of corticosteroids in fetus with growth restriction has been raised because in that special case, an increased risk of cardiometabolic disease can be related to the growth restriction. According to previous animal studies, an exacerbation of fetal cardiovascular dysfunction may be due to an antenatal administration of betamethasone (Miller et al., 2009). It seems therefore necessary to investigate the safety of the use of antenatal corticoids in this setting. An observational study reported a short stature in childhood related to early fetal growth restriction (Schaap et al., 2001).

Children whose mother participated in the Australasian Collaborative trial of Repeat Doses of Corticosteroids have been closely exanimated in order to evaluate if repeating betamethasone courses may cause cardiometabolic disease occurring in childhood, especially at 6 to 8 years. In this trial the benefits of repeated course antenatal corticoids have been identified such as a reduction of the incidence and severity of lung disease and neonatal morbidity. The focus of this study was basically on the examination of body composition, insulin sensitivity, ambulatory blood pressure and renal function in order to evaluate changes of risk factors for cardiometabolic disease. Children

whose mother was exposed to repeat antenatal betamethasone showed very similar outcomes compared to the placebo group. For example, total fat mass was similar (geometric mean ratio 0.98, 95% confidence interval [CI] 0.78 to 1.23). No differences of the 24-hour ambulatory blood pressure between the two groups has been found (mean difference systolic 0 mm Hg, 95% CI −2 to 2; diastolic 0 mm Hg, 95% CI −1 to 1). Finally, the estimated glomerular filtration rate was also similar (mean difference 1.2 mL/min/1.73m^2, 95% CI −3.2 to 5.6). According to these finding repeating the course does not increase risk factors for cardiometabolic disease (McKinlay et al., 2015).

In animal studies, repeated glucocorticoids may lead to an impairment of fetal calcium uptake and mineralization and alter postnatal appendicular growth (Moss et al., 2003, (Mosier et al., 1981; Swolin-Eide et al., 2002). Musculoskeletal growth is regulated by several hormones such as leptin and insulin-like growth factors (Ahmad et al., 2006; Marinoni et al., 2008). Glucocorticoids may influence the concentrations of these hormones and the cortisol secretion which in turn leads to a bone loss (Reynolds et al., 2005). It has been supposed that growth restriction and consequently osteoporosis was due to a greater exposure to antenatal corticosteroids. In order to investigate the potential association between repeated glucocorticoid admission and altered bone mass, a whole-body-dual-energy radiograph absorptiometry has been performed in children whose mothers participated in the ACTORDS. The findings resulted that whole-body bone mineral content, bone area and the incidence of fracture were similar for those children exposed to repeated administration and those belonging to the placebo group. No adversely effects on bone mass were evident in children at 6 to 8 years´ corrected age after repeated treatment of betamethasone. Therefore, a repeated course does not alter bone growth, peak bone mass or the mineralization of spinal trabecular bone which is affected in osteoporosis. Even after a single treatment of betamethasone boss mass was not affected (Stuart R. Dalziel et al., 2006). However, it is not fully known why these discrepancy of the findings between animal and human studies. Interspecies differences in organ development or dose depending effects may be influencing the outcomes. A limiting role of glucocorticoids in the programming of osteoporosis could also not be excluded (McKinlay, Cutfield, et al., 2017).

Furthermore, Crowther et al. evaluated the related benefits and risks of repeated doses of antenatal corticosteroids in mid-childhood. They compared outcomes from children, from 6 to 8 years, antenatally exposed to placebo with those exposed to multiple courses of betamethasone. It has

been concluded that no differences between those two groups regarding neurodevelopment, including cognitive function, body size, blood pressure, spirometry and health-related quality of life have been noted.

To conclude repeat doses of ACS is considered to have no significant harm in early childhood (Crowther et al., 2015)

Maternal outcomes after multiple doses of ACS

In the Cochrane Database review, additionally, maternal outcomes of a repeated antenatal betamethasone treatment have been reported. It has been found that no increase in infectious morbidity of chorioamnionitis occurred. These findings are very satisfying because chorioamnionitis is one of the pathologies associated with the development of brain lesions in small premature babies. Furthermore, puerperal sepsis has also increased due to a repeated administration. According to World Health Organization (WHO) this infection is furthermore one of the main causes of maternal death. There has been concerns about repetitive betamethasone treatment in pregnancies complicated by PPROM and it has been proved that no adverse event on chorioamnionitis and early onset sepsis have been found (Smrcek et al., 2005). Besides Magann et al (2017) reported that there was no increase of neonatal sepsis found after repeating the treatment. In a randomized controlled it has been proved that multiple antenatal betamethasone administration was not associated with a higher risk of adverse maternal or neonatal outcomes such as fever or chorioamnionitis or neonatal sepsis (Thorp et al., 2001) . Women exposed to repeated courses of antenatal betamethasone are more likely having insomnia. 2.3% of the repeat prenatal corticosteroid group compared to 0.8% of non-treated group had insomnia. In one trial a reduction in bruising at the injection site was reported for women exposed to betamethasone compared to those exposed to placebo. To conclude, no changes of the likelihood of Caesarean birth have been noticed after repetitive administration of this glucocorticoid.

The administration of multiple courses could be associated with both maternal and fetal pituitary-adrenal suppression (Crowther et al., 2015).

6.1.14. ALTERED ROUTE

The standard route of ACS treatment is currently a maternal intramuscular injection with a transplacental transfer to the fetus (Roberts et al., 2017). It was considered to change the route in an attempt to minimize either the potential side effects of the mother and the fetus. Actually, intramuscular fetal injection has already been administrated as a paralyzing agent before intravascular blood transfusions in cases of fetal anemia (Schumacher & Moise, 1996).

According to one of the first animal study, a significant improvement in postnatal lung function has been found after direct intramuscular injection in the fetus 48 hours before birth (Jobe et al., 1993). 10 years later Moss et al. (2003) conducted an animal study and compared pharmacokinetics of betamethasone after maternal intramuscular exposure with pharmacokinetics findings after a direct fetal intramuscular injection in order to evaluate the performance of the alternative route. A direct intramuscular injection of betamethasone into the fetus has been performed under ultrasound guidance in fetus of 10 pregnant ewes. Fetal peak concentration was 341.2 ±23.7 nmol/L and was detected within 30 minutes after direct intramuscular injection of betamethasone. The chosen dose was 0.5 mg per kg body weight. The rapid peak concentration in fetal circulation after direct fetal exposure is not sustained. But when betamethasone has been administrated in the muscle of the mother, the fetal peak concentration of betamethasone was 37.6 ±3.7 nmol/L ($P<0.001$) which is clearly not in the same dimension compared to the direct fetal injection. Peak concentration gradually raised between 1 and 4 hours after injection. It has been found that 4 hours after maternal injection fetal plasma concentration were superior to plasma concentration 4 hours after direct fetal concentration. Compared to the commonly established treatment, direct fetal intramuscular exposure resulted a higher fetal plasma concentration of this corticosteroid. When betamethasone has been injected directly into the fetus's muscle, the half-life of betamethasone was 1.1 ± 0.3 hours and deferred significantly from the half-life of betamethasone after maternal injection, which was 8.5 ±2.0 hours; ($P= 0.006$). Greater cumulative fetal exposure has been noted especially when dexamethasone has been directly injection in the fetus muscle. Even though the peak concentration was minor after maternal injection, the applied doses still lead to growth restriction (Ikegami et al., 1997). It has been found that direct fetal intramuscular injection may not cause growth restriction and no apparent deleterious effects are found even after repeating the treatment for 4 weeks (Moss et al., 2001; Newnham et al., 1999). Larger peak concentration of betamethasone has been detected after direct fetal administration, but the duration of the fetal exposure was shorter. Moss et al.

highlighted that adverse effects on fetal growth may be associated with repeated and prolongated exposure to corticosteroids. The different fetal growth responses may be primary related to the duration of the exposure (Moss et al., 2003).

In another animal study it has been found that repeating the administration neither cause growth restriction nor reduce fetal birthweight and weight or major organs (Newnham 1999).

In a single arm trial in human, intramuscular injection in the fetus has been performed in 6 women at risk of preterm birth and in 5 cases an improvement of lung maturation has been found (Ljubić et al., 1999). This altered route resulted an increase in fetal breathing and no changes in fetal movement (Babovic 2009). A major advantage is that the passage through the placenta is bypassed, making medication more efficient due to a more rapid lung maturation (Evan 1993).

The alternative route of application may be beneficial for the mother health by preventing the risk of increased blood pressure, increased blood glucose level and susceptibility to sepsis in the mother. A reduced concentration of corticosteroids may be needed in order to induce lung maturation.

This treatment is feasible (Utama & Crowther, 2018).

Nevertheless direct fetal injection is associated with potential risks which should be weighed against relative benefits in order to justify the use of this route. Specific issues addressed are for instance that preterm labor can be initiated by the direct fetal injection (Newhanham 1999). Fetal injury, placental abruption, amniocentesis, maternal fetal hemorrhage and pregnancy loss (RCOG 2010) are potential risks after direct fetal exposure to corticosteroids. The risk of uterine infection and PPROM cannot be excluded under these circumstances. There is an increased risk of preterm birth which is associated with high neonatal morbidity and mortality (Evans 1993; (Goldenberg et al., 2008)

There are no current studies performed yet comparing direct injection into the fetus to maternal intramuscular administration. It is therefore necessary to perform randomized controlled trials focusing and the related harms or benefits of the different routes. It is still recommended to stay with the current standards due to a lack of good quality data on health outcome regarding the direct fetal injection of betamethasone (Utama & Crowther, 2018).

6.1.15. INTERACTIONS

The interactions between betamethasone and other drugs have been listed below (Fachinformation, Celestan biphase).

Cardiac glycosides	Enhanced mechanism of action of corticosteroids because of a lack of potassium.
Saluretic agents, Amphotericin B	Additional potassium excretion.
oral Antidiabetics	Blood sugar reduction is reduced.
Coumarin-Derivatives	Anticoagulant effect is weakened.
Barbiturate, Hydantoin, Rifampicin, Ephedrine	Corticosteroid effect is reduced.
Estrogen	Corticosteroid effect is enhanced.
Aspirin	Aspirin is known to cause stomach upset and glucocorticoids can mask these adverse effects. The mechanism is unknown. An increased risk of gastrointestinal bleeding and ulcer are found. Glucocorticoids reduce the effect of salicylates.
NSAIDs	Increased risk of gastrointestinal bleeding, increased risk of Stomach and duodenal ulcers because glucocorticoids lead to an increased HCl secretion.
ACE-Inhibitor	Risk of the occurrence changes of blood count.
Chloroquine, Hydroxychloroquine, Mefloquine	Increased risk of myopathy and cardiomyopathy.
Ciclosporin	Both the effect of corticosteroids and ciclosporin is enhanced
Isoniazid	Corticosteroids lead to an increased clearance of isoniazid.
Growth hormones	A weakening of the effect of growth hormones is possible.
Ketoconazole	The effect of ketoconazole is enhanced.

Bupropion	Simultaneous administration with systemic glucocorticoids may increase the risk of seizures.
Methotrexate	Enhanced effect of glucocorticoids. (the mechanism is unknown)
Protirelin	Thyroid Stimulation Hormone (TSH) is reduced.
Antibiotics	It is reported that macrolide antibiotics cause a significant reduction in corticosteroid clearance.
CYP3A-Inhibitor	Simultaneous treatment with CYP3A inhibitors is expected to increase the risk of systemic side effects because the metabolism of glucocorticoid is inhibited. The combination should be avoided unless the benefits outweigh the increased risk of systemic side effects of corticosteroids.
Vaccines	Glucocorticoids have an immunosuppressive effect and therefore vaccines should be avoided.

Macrolide antibiotics are often used in suspected infections in relation to preterm birth.
Macrolide antibiotics inhibit CYP3A4 and therefore lead to a decrease of betamethasone clearance (drugs.com, Westphal, 2000).

6.1.16. OTHER INDICATIONS FOR TREATMENT IN PREGNANCY

Glucocorticoids are used to substitute restricted production of the maternal adrenal cortex during pregnancy and are not associated with any risk to either mother or child. Higher doses are used in antiallergic or antiphlogistic therapy. It has been found that oral cleft formation occurred in only 1 in 1 000 newborns and the overall malformation rate is 3-5% under systemic glucocorticoid therapy. According to Oren et al 2004 it is recommended that long-term systemic glucocorticoids administration to the mother in the 1st trimester should be followed by a detailed sonographic diagnosis (Oren et al., 2004). However, non-halogenated glucocorticoids such as prednisolone and prednisone are favorized because they are less likely to pass through the placenta. In the treatment of allergic reactions, a dose of 0.5-2 mg/kg body weight and the maintenance dose is 0.3-0.5 mg/kg body weight has been used. In case of shorter treatment, higher doses can be used. For instance,

500-1000 mg of prednisolone per day for 5 days can be used to treat a relapse of encephalitis disseminate (Paulus, 2016).

Use of Dexamethasone in case of Adrenogenital Syndrome in pregnancy

Congenital adrenal hyperplasia is inherited autosomal recessively and occurs with an incidence of 1:12000. This is caused by a defect of 21-hydroxylase and thereby the metabolism from cholesterol to cortisol is prevented. An increase ACTH secretion follows and leads to excessive 17-hydroxyprogesterone accumulation in the adrenal glands. 17-hydroxyprogesterone convertes into androstenedione and testosterone. Dexamethasone is used to achieve a suppression of the fetal adrenal cortex in order to reduce androgen production. 3 doses of 0.5mg or 20-25 µg/kg body weight are distributed over three daily doses, used in the 6th week post menstruation. As a therapy control, the mother's serum is checked for cortisol and estriol, which serve as markers of maternal and fetal adrenal cortex function, for 4 weeks (Gembruch & Geipel, 1999) . This therapy is performed if both parents are homozygous or heterozygous carriers and if there is a confirmed lack of fetal 21-hydroxylase. In female and homozygous carriers, therapy is continued until birth in order to reduce the elevated androgen level leading to virilization of the external genitals, clitoral hypertrophy and even intersexual genitalia. Through the use of dexamethasone, expensive corrective surgery could be avoided (Kohl & Gembruch, 2016) .

6.2. TOCOLYSIS

The onset of premature labor is one of the main symptoms of preterm birth, it usually occurs with a frequency of 4 or more contractions per hour. The performance of a tocolysis hereby includes a temporary prevention or reduction of the frequency of these contractions. But the underlying cause is not eliminated by a tocolysis.

Tocolytic agents are used to inhibit uterine contractions enough to prolong a pregnancy for a few days. On one hand, the aim is to gain enough time in order to allow the administration of a completed ACS course and on another hand to assure the transfer to a perinatological center. Further, the intravenous administration of high doses of magnesium for neuroprotection of the fetus can be achieved. In fact, a so-called short term tocolysis aims to prolong the pregnancy for 48h. As a consequence, a longer exposure to tocolytic agents have been considered in order to inhibit contractions for a longer time or even to prevent preterm birth. However, there is a lack of evidence that tocolysis treatment longer than 48 hours may improve neonatal morbidity.

Tocolysis is indicated in case of the occurrence of premature contractions ≥ 4 /20 min accompanied by a shortening of the cervical length and/or by an opening of the cervix. Absolute and relative contraindications to tocolysis are the following: fetal malformation, severe pre-eclampsia/eclampsia, maternal bleeding, intrauterine infection/ chorioamnionitis, fetal hypoxia, premature placental abruption and a cervical dilatation above 4 cm. This intervention is not recommended before 22 + 0 week of gestation and rarely given after 34 + 0 weeks of gestation (Leitlinienprogramm DGGG OEGGG SGGG, 2020).

The main tocolytic drugs include ethanol, betamimetics, cyclooxygenase inhibitors, calcium channel inhibitors and oxytocin receptors inhibitors.

6.2.1. ETHANOL

Ethanol was one of the earliest tocolytic agent used to delay birth for women in preterm labor. This treatment is no longer used in current practice because it has been considered that maternal and fetal risks outweighs benefits.

6.2.2. BETAMIMETICS

Betamimetics are agonists of the β2 adrenergic receptor, which is a guanine nucleotide binding protein. This membrane protein is a heterotrimer and its alpha subunit belongs to the Gαs family and is responsible to the activation of the effector enzyme adenylate-cyclase which catalyzes the cyclisation of ATP to cAMP. This results in an increase of the intracellular cAMP concentration which may cause the inhibition of the myosin light chain kinase phosphorylating smooth muscle myosin and lastly avoid contraction. Thereby, relaxation of the smooth muscle has been promoted. (Klabunde 2012) There is a decrease of involved receptors during tocolysis.

Fenoterol and Hexoprenaline are most commonly used in German-speaking countries whereas Ritodrine and Terbutaline are preferred in anglophone countries. These betamimetics are commonly used in order to assure bronchodilatation due to its broncho-spasmolytic effect. Because of their relaxing effect on the smooth muscle, it has been considered that this drug class can be administrated in order to assure tocolysis.

According to the metanalyses including 20 studies, it has been concluded that beta mimetics may decrease the rate of preterm birth occurring within 48 h and even within 7 days (Neilson et al., 2014).

A major side effect is maternal and fetal tachycardia, which can be considered as a limiting factor of the use of betamimetics. Therefore, close monitoring in the form of an electrocardiogram (ECG) should be performed when betamimetics are administrated. Further, these following side effects have been listed: maternal chest pain, dyspnea, palpitation, tremor, headaches, hypokalemia, hyperglycemia, nausea or vomiting, nasal stuffiness. An additional interaction with β 1 receptors may be considered to be the leading cause of side effects such as tachycardia and palpitations. Further, the administration of betamimetics may cause lung edema (de Heus et al., 2009). Multiple pregnancies, infection and inflammationas well as preeclampsia lead to increased fluid retention in the maternal circulation and thus represent an increased risk of the formation of pulmonary edema (Clesham, 1994). Contraindications of this therapy are cardiac arrhythmia, cardiac surgery in mother or fetus, hyperthyroidism and poorly controlled diabetes mellitus.

Fenoterol has a short half-life of 22 min. 25 μg Fenoterol is injected intravenously within 2 to 3 minutes and is followed by an infusion up to 4 μg/min. Also, intravenous infusion of fenoterol (0.5-3 μg/min) can be given in case of imminent preterm birth (Leitlinienprogramm DGGG OEGGG SGGG, 2020). Hexoprenaline, in turn has a greater specificity for beta 2 receptors and may

therefore be better tolerated. These drugs should not be given orally or rectally. Fewer maternal and fetal side effects have been noted after a bolus application of β-mimetics. Therefore, this dosage regiment seems to be preferable in German-speaking countries.

The use of betamimetics is no longer recommended as this treatment is associated with the greater rate of maternal and fetal side effects (Leitlinienprogramm, DGGG, ÖGGG, SGGG, 2020; (Haas et al., 2012).

6.2.3. OXYTOCIN RECEPTOR ANTAGONIST

Oxytocin is a cyclic nonapeptide released from the posterior pituitary. This hormone interacts with the oxytocin receptor, a Gq/G11-coupled receptor, expressed on the membrane of the smooth muscle cells of the myometrium and on the mammary gland epithelium. Oxytocin promotes milk ejection at the end of pregnancy and during lactation. This hormone may influence the mood and the development of the mother-child relationship. More importantly, it plays a major role in the onset of labor. It has a direct contraction triggering or amplifying effect on the smooth muscles of the myometrium. The interaction with the membrane receptor leads to an opening of the calcium channels in the cell membrane and thus to an increased influx of ionized calcium from the extracellular space. Also, this stimulation of the oxytocin receptor results in a release of calcium from intracellular storage. It stimulates also the synthesis and release of prostaglandins, which in turn sensitize the myometrium to oxytocin. An increase in oxytocin receptor density by the factor 150 is characterized near term and therefore the myometrium is more sensitive. This emphasizes that the increased sensitization of the myometrium is actually decisive for the labor-stimulating effect of oxytocin (Helmer and Schneider, 2015).

Atosiban actually is the only drug among the other tocolytic agents which has been developed for this indication. This drug works like a competitive antagonist. Chemically speaking, it is an oxytocin-analog, [1-Desamino-2-D-Tyr(Et)-4-Thr-Orn]-Oxytocin.The potency of atosiban at the human oxytocin receptor is lower than that of oxytocin. Besides, it has a greater affinity to the vasopressin v1a receptor and thus prevents the effect of vasopressin (Förstermann et al., 2013). Due to the binding to the receptor in the decidua and in myometrium, the influx of ionized calcium into the cells has been inhibited (Goodwin et al., 1996).

The use of atosiban has been approved in order to delay an imminent preterm birth between 24+0 to 33+6gestational weeks (Leitlinienprogramm DGGG OEGGG SGGG, 2020). 6.75 mg are given

within 1 min intravenously as a bolus, followed by an infusion of 18mg/h during 3h and then 6mg/h for up to 45 hours. Its half-life is about 13 min (Helmer & Schneider, 2016).

It has been demonstrated that atosiban was considered to be superior to placebo and other tocolytic agents such as beta-memetics or calcium channel antagonists in order to prolong pregnancy and to improve neonatal outcome (Flenady et al., 2014).

Side effects including nausea, vomiting can be observed when the oxytocin receptor antagonist has been used. As therapeutic concentrations are mainly found in uterine tissues and in the mammary gland epithelium, there are only minor cardiovascular side effects.

The use of atosiban is supported by the fact that there were significantly fewer maternal side effects in relation to this medication. The occurrence of serious side effects is significantly lower when atosiban is administered, compared to betamimetics and to nifedipine (Moutquin et al., 2000; van Vliet et al., 2016). Most importantly, the fetal and neonatal mortality was lower in the atosiban group. This supports the use of this oxytocin receptor antagonist over betamimetics (Husslein et al., 2007). Furthermore, therapy terminatio due to side effects was very low (only 1%) which underlines the increased tolerance compared to beta-agonist (Flenady et al., 2014).

To conclude, atosiban is considered to be the first line tocolytic agent. It can be used alternatively when both nifedipine and indomethacin are contra-indicated. Oxytocin receptor antagonists are not approved for tocolysis > 48 hours due to insufficient data. (Leitlinienprogramm DGGG OEGGG SGGG, 2020) Furthermore atosiban seems to be the most adequate choice in case of maternal cardiac diseases, hyperthyroidism, gestational diabetes or multiple pregnancy (Helmer & Schneider, 2016).

6.2.4. CALCIUM CHANNEL BLOCKERS NIFEDIPINE

Voltage-dependent calcium channels of L-type are exposed on the membrane of cardiomyocytes and lead to an increase in intracellular calcium concentration.

Nifedipine belong to the dihydropyridine, which bind preferentially to the inactivated state of the channel. Nifedipine binds directly to the alpha 1 c subunit of the Ca channels, thereby blocking the inflow of calcium. In therapeutic dosage dihydropyridines have an effect on the smooth vascular musculature, especially on the arteries and arterioles including the coronary arteries where they induce relaxation. A major advantage of the use of this type of calcium channel blockers is that

contraction of heart muscle remains unaffected. This drug is commonly indicated for the treatment of hypertension, because it has been shown to reduce the total peripheral resistance.

Further, the drug can be used in tocolysis because it has been found that nifedipine inhibits selectively the uterine contraction (Granger et al., 1985).

Intracellular calcium concentration influences the activity of myosin light chain kinase, which is the key enzyme involved in the onset of smooth muscle´s contraction. Due to the inhibition of the influx of calcium ions, this enzyme is not able to catalyze the phosphorylation which is decisive for the initiation of contractions. Calcium channel inhibitors may also inhibit the release of calcium out of the intracellular storage and stimulate the efflux of calcium ions out of the cell.

According the Cochrane Review, nifedipine has benefits over betamimetics regarding the prolongation of pregnancy (Flenady et al., 2014). Another positive aspect is that these drugs may be less expensive (Hayes et al., 2007). Further, serious neonatal morbidity such as RDS, IVH, NEC and maternal adverse effects are less observed when calcium channel blockers have been used (Flenady et al., 2014). This supports the use of these tocolytic agents over beta mimetics.

The only issue remains to identify optimal dosage regimen and formulation in order to improve the treatment. 10 mg of nifedipine is taken orally every 15 min followed by 20 mg given every 4h. After 48h, the dose is reduced to 10mg given every 8h. The half-life of nifedipine is 2-3h and the maximum plasma concentration after taking a 20 mg tablet is reached after 30-60 minutes. The daily maximal dose is 150 mg. Due to a rapid onset of effects a strong hypotensive effect may result. Therefore, a sublingual administration should be avoided (Rodts-Palenik S, 2000). The combination with magnesium (i.v.) may cause a neuromuscular blockage. Due to a systematic vasodilatation side effects including tachycardia, flush, headache, palpitations may be noted. Therefore, a close monitoring of the blood pressure should accompany the medication. Further vertigo and pulmonary edema also may be associated with the administration (Ferguson et al., 1990). There are no negative fetal effects related to the treatment.

It is not recommended to use nifedipine for maintenance therapy after pulmonary maturation has been achieved, as neither prolongation of pregnancy nor improvement of neonatal parameters has been demonstrated (Naik Gaunekar et al., 2013). The maximum daily dose of 60 mg should not be exceeded, as this results in a 3-fold increase in the rate of tachycardia and a 9-fold increase in the frequency of hypotension (Leitlinienprogramm, DGGG OEGGG SGGG, 2020). Abrupt hypotension with consecutive fetal hypoxia may be observed after sublingual administration. This route should be avoided (Impey, 1993). Not only the route plays a significant role but also the

formulation of the drug substance. Slow release preparations can also lead to persistent hypotension (Stones, 2016). A hypotension of less than 90/50 mm Hg is considered to be a contraindication of this treatment. In fact, the administration of dihydropyridines leads to a rapid reduction in blood pressure what in turn induce reflex tachycardia and activation of the renin-angiotensin system. Special precautions should be taken in pregnant women with known hypotension and pre-existing cardiovascular disease (Leitlinienprogramm DGGG OEGGG SGGG, 2020). Also, the combination with antenatal corticosteroids may cause pulmonary edema. Blood pressure and heart rate should be closely monitored during treatment (Oei, 2006)**.**

CYP Polymorphism may alter nifedipine´s clearance. It seems therefore relevant to include pharmacogenetic data into the therapy in order to improve the treatment in pregnancy (Haas et al., 2013).

Nifedipine is metabolized by CYP 450 3A4. An increase in the plasma concentration and thus an increase in the effect of nifedipine may be observed when erythromycin is additionally used (see Chapter 6.4. Antibiotics). Nifedipine is almost completely metabolized in the liver (high first-pass effect). In case of impaired liver function, there is a significant increase in the elimination half-life and a reduction in overall clearance. A dose reduction may be necessary (Embryotox.de,Nifedipin).

There is no official approval of the drug for this indication.

6.2.5. NITRIC OXIDE DONOR

The vascular endothelium influences blood flow and vascular dilatation by releasing substances that locally affect the tone of the smooth vascular muscles. Nitric oxide is an important vasodilator. NO is formed from the guanidino group of the amino acid L-arginine under catalysis by the enzyme NO-synthase. Once it diffuses into the vascular muscle cell, it reacts intracellularly with the guanylyl cyclase in the cytosol. An increase cGMP level is found in the cell. The intracellular cyclic nucleotide cGMP is with cAMP an important mediator of smooth muscle relaxation. In fact, cGMP activates protein kinase G (PKG) which in turn after being phosphorylated activate myosin phosphatase. This induce relaxation if the smooth vascular muscle. The organic NO glyceryl trinitrate is used for the treatment of angina pectoris. It is also used as an antispasmodic for the treatment of biliary colic. Nitroglycerin is applied transdermally to induce inhibition of contractions. 1 to 2 plasters of 10 mg each for 24 hours are applied.

The use of nitroglycerin <34 and <37 weeks of gestation may lead to a reduced rate of preterm birth compared to beta agonists (Agustín Conde-Agudelo & Romero, 2013). A reduced risk of neonatal morbidity and mortality may be also related to the treatment (Smith et al., 2010). This treatment is however associated with more frequent maternal side effects (Kashanian et al., 2014).

The associated side effects are actually very similar to those observed when calcium antagonists have been used. These includes hypotension, vertigo, redness of the skin, palpitations. Paracetamol may be used in case of nitrate headaches (Schleussner et al., 2003).
Even if the use of NO may be superior to betamimetics, it has been pointed out that there is no sufficient evidence to support the use of NO as a tocolytic agent.

6.2.6. CYCLOOXYGENASE INHIBITORS

Cyclooxygenase inhibitors are well-known prescribed drug in the treatment of pain, fever, swelling from inflammation. The drug of choice is an unspecific inhibitor named indomethacin which belongs to the nonsteroidal anti-inflammatory drug (NSAID). This drug is also indicated in pregnancy. The cyclooxygenase catalyzes the conversion from arachidonic acid to prostaglandin-H in amnion and chorion. An increase in the expression of the COX 2 in the decidua and myometrium is evident in preterm labor (Helmer & Schneider, 2016). Glucocorticoids, CRH and cytokines such as Il-1 may influence the synthesis of prostaglandin which in turn plays an important role in the onset of preterm labor, in uterus contraction and cervix maturation (Challis et al., 2000). Prostaglandins stimulate the formation of gap junctions, the transmembrane influx of ionized calcium into the cell and the release of calcium from the intracellular storage, the sarcoplasmic reticulum. Prostaglandin synthesis inhibitors lead therefore to a decrease of an intracellular calcium level. These drugs may also have an anti-inflammatory effect which seems also very relevant as inflammation may influence preterm labor. Compared to betamimetics, indomethacin is superior in order to lead to prolongate pregnancy (King et al., 2005).
According to the findings from a Cochrane review, the use of indomethacin leads to a reduction in birth within 48 hours and in preterm birth occurring before 37 gestational weeks. The treatment had no impact of neonatal morbidity and mortality. Concerning fetal or neonatal outcomes and prolonging pregnancy, COX inhibitors scored similar to calcium channel blockers (Reinebrant et al., 2015).

The therapy starts with 50 mg p.o. and is followed by 25 mg p.o. every 4-6h. Another possibility to initiate the therapy is to give 100 mg rectally. It should be noted that specific COX 2 inhibitor such as rofecoxib may not show effects in prolongation the pregnancy in women with premature labor (McWhorter et al., 2004). The use of cyclooxygenase inhibitors is associated with the following side effects: nausea, gastritis symptoms, headache, vertigo, ringing in the ears. There are however fewer side effects when this tocolytic agent has been used. Contraindications for this treatment are stomach ulcus, kidney and life damage, thrombocytopenia and coagulation disorders. Indomethacin has the ability to cross the placenta barrier and therefore reaches the fetus circulation. It´s half-life is at preterm 19h. Occlusion of the ductus arteriosus is one of the main fetal adverse effect related to the treatment with indomethacin. Further, the treatment for more than 48 hours appears to be a particular risk factor. Therefore, this drug should be taken before 32 + 0 weeks of gestation and within 48 h in order to avoid the risk of premature closure of ductus arteriosus (Reinebrant et al., 2015). Cyclooxygenase inhibitor may lead to a reduction of fetal urine production. Oligohydramnion has been noted in 10% of the cases, which however seems to be reversible 96 h after the treatment (di Renzo et al., 2017). Contraindications of this treatment are as a consequence fetal heart defects and oligohydramnios. There is an increased risk of neonatal complications such as NEC and IVH if the exposure lasts more than 72 h. increased neonatal mortality was also not identified (Loe et al., 2005).

The combination of different tocolytic agents has not been confirmed due to insufficient evidence. It may be possible that this strategy may lead to an increased risk of potential side effects. However, it seems possible to switch to another tocolytic agent if no satisfying effects have been noted (Vogel et al., 2014) Nifedipine, atosiban, indomethacin are preferably used to perform a tocolysis. Actually, atosiban is the only drug especially designed for this indication and is considered to be the most expensive drug among the other tocolytic agents. According to Wex et al. who conducted an economic evaluation of the treatment with atosiban compared to betamimetics, the sum of hospital costs with atosiban is nevertheless lower than with fenoterol (Wex et al., 2009). Calcium antagonist also has advantages, as it leads to a reduction in potential side effects compared to betamimetics. Further, the orally application is considered to be beneficial and therefore the use of calcium channel antagonist has been supported once again. There is no evidence from randomized controlled trials to recommend the use of tocolytics in extreme preterm birth, multiple births and intrauterine growth restriction. Further, it is not recommended to perform a long lasting tocolysis

to reduce the incidence of preterm birth and decrease mortality and morbidity. Progesterone should not be used following tocolysis in order to maintain the pregnancy and to prevent preterm birth (WHO, 2015). To conclude, individualized therapy should be performed and therefore the choice of the drug should be based of the patient-specific characteristics.

6.3. MAGNESIUM SULFATE

A separate chapter is devoted to the use of magnesium sulfate, because it no longer has any relevance as a tocolytic agent. According to a Cochrane review it has been concluded that this drug is not suitable as a tocolytic agent. It has been demonstrated that magnesium sulfate neither lead to prolongate pregnancy for more than 48h nor reduced the rate of preterm birth. Additionally, magnesium sulfate may increase the risk of total fetal, neonatal or infant mortality. Efficacy of this drug is dose-dependent, which may influence the incidence of maternal side effects. To conclude, according international guidelines this treatment is no more indicated for tocolysis (Crowther et al., 2014).

Magnesium sulfate plays a major part in the protection of immature brain. This is certainly relevant because neurological injury may be associated with preterm birth.

Magnesium acts as a non-competitive blocker of the **N**-methyl-d-aspartate (NMDA) glutamate receptor and influence calcium influx what in turn may prevent apoptosis. It is also involved in the nerve impulse conduction due to for example its inhibiting action on calcium channel, its modulating action on ion pumps (e.g., Na+/K+ ATPase). Further, due to its anti-inflammatory properties, magnesium reduces oxidative stress and the production of pro-inflammatory cytokines. Regarding its biochemical effects, this drug appeared to be appropriate for neuroprotection.
The Cochrane Review aimed to assess the effects of magnesium sulphate in neuroprotection and it has been found that the risk of cerebral palsy in children antenatally exposed to magnesium was substantially reduced (RR 9.68; 95% CI 0.54 to 0.87, five trials, 6 145 infants). Also, the rate of substantial gross motor dysfunction (RR 0.61; 95 CI 0.44 to 0.85) was significantly reduced. These

finding may underline the neuroprotective effect of magnesium sulphate antenatally administrated (Doyle et al., 2009).

Cerebral palsy can be prevented by the administration of magnesium sulphate (Shepherd et al., 2017). Additionally, it has been found that magnesium sulphate may prevent cerebral palsy at 2 years (Chollat & Marret, 2018).

According the WHO, it is recommended to use magnesium sulfate in order to prevent cerebral palsy. This treatment is indicated for women with singleton and multiple pregnancies who are risk of imminent preterm birth before 32 + 0 gestational weeks. More precisely, the use of magnesium sulfate is only appropriated when preterm birth is likely within the next 24 hours. Since magnesium is eliminated via the kidney, special caution is required in patients with renal insufficiency.

It is recommended to administrate a bolus of 4-6 g over 30 min and is followed by a maintenance dose of 1-2 g for 12h in order to double the maternal magnesium level. It is possible to repeat the administration if the birth does not occur within 12 h. Flush, sweating, nausea, vomiting or problems at the injection site are among the most frequently observed maternal side effects of systemic magnesium therapy. A 50% higher risk of hypotension and tachycardia were also associated with the treatment (number needed to harm (NNH): 28 - 30) (Berger et al., 2019).

It seems necessary to mention that the combination of magnesium sulfate and nifedipine may cause potential side effects including hypotension and respiratory depression. Therefore, another tocolytic agent such as indomethacin should be preferred in parallel to neuroprotection (NICE, 2015) Further, in case of PPROM, this treatment is not recommended.

However, the administration of magnesium sulfate is considered to be safe, cost-effective, feasible and is shown to be efficient in order to improve neurological outcomes (Chollat & Marret, 2018).

6.4. ANTIBIOTICS

It has been shown that penicillin, cephalosporine and macrolide are the most commonly used antimicrobial agents in term of maternal and fetal safety (Crider et al., 2009). Indication for

antibiotic treatment is to improve the neonatal outcome by prophylactically giving to prevent fetal infection. It has not been proven that antibiotic treatment prolongs pregnancy.

In this regard, it has now been questioned whether antibiotics can also be used to prolong pregnancy. Kenyon et al. conducted the ORACLE II study which included 6295 women with premature labor with intact membranes and without the evidence of clinical infection. 250 mg erythromycin (n=1611), 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid; n=1550), both (n=1565) or placebo (n=1569) have been given to the patients 4 times daily for 10 days. It has been concluded that the administration of antibiotics in women with premature labor and no rupture of membranes may not influence the duration of pregnancy. It has been noted that antibiotic administration lead to a reduction of maternal infection. The use of antibiotics in cases of premature labor without rupture of membranes is not recommended (Leitlinienprogramm DGGG OEGGG SGGG, 2020).

It has been proposed that the use of antibiotics to prevent the cause of the contractions. Intrauterine infections also influence the onset of premature labor and may be considered as a quite relevant risk factor. It has been supposed that preterm labor may be associated with ascending lower genital tract infections. Actually, cytokines may trigger prostaglandin synthesis in chorion which in turn result in the onset of preterm labor (Basavaprabhu et al., 2020).

The use of antibiotics may have positive effects in women with preterm premature rupture of membrane (PPROM). In the ORACLE I study, either 250 mg erythromycin (n=1197), 325 mg co-amoxiclav (250 mg amoxicillin plus 125 mg clavulanic acid; n=1212), both (n=1192) or placebo (n=1225) have been given to 4826 women with PPROM. It has been found, that erythromycin may lead to a prolongation of pregnancy. Further, it can be considered that this antibiotic may improve early neonatal outcome. Less surfactant has been used and the neonate was less dependent of oxygen at 28 days of age and older. Additionally, fewer major abnormalities on ultrasonography before discharge and fewer numbers of positive blood culture were noted after the exposure with erythromycin. The use of antibiotics may be associated with a prolongation of pregnancy and with a reduction of maternal and neonatal infection. Moreover, this treatment leads to a reduction of gestational age dependent morbidity after PPROM. A significantly higher rate of NEC has been noted when co-amoxiclav only and co-amoxiclav plus erythromycin have been administrated (S. L. Kenyon et al., 2001). A Cochrane review underlined that routine prescription of antibiotics may

prolong pregnancy and improve neonatal short-term outcomes and may decrease perinatal mortality (Sara Kenyon et al., 2013). An optimal regimen of antibiotic treatment has not been published. The treatment can be initiated with the intravenous administration of 2 g ampicillin every 6-8h over 2 days, then 3x 500 mg or 2 x 875 mg amoxicillin can be given orally over 5 days. Additionally, 1 g of azithromycin should be administrated orally as a single dose. This following regimen has been associated with a reduction of perinatal morbidity after PPROM: ampicillin 2 g i.v. every 6 h and erythromycin 250 mg i.v. every 6 h for 48 h followed by amoxicillin 250 mg p.o. every 8 h and erythromycin 333 mg p.o. every 8 h for 5 days (Mercer et al., 1997). Macrolides such as erythromycin and azithromycin seem to be suitable for treatment against genital mycoplasma causing chorioamnionitis in PROM.

Furthermore, asymptomatic bacteriuria which is a bacterial infection without any of the typical symptoms, may also be considered as a significant risk factor for preterm birth and contribute to a reduced birthweight. In a Cochrane Review, it has been supposed that the antibiotic treatment may be associated with a reduced risk of pyelonephritis (Smaill & Vazquez, 2019). However, due to a lack of data, it remains unanswered whether antibiotic treatment of asymptomatic bacteriuria seems to be appropriated. Screening is not currently recommended when the sole purpose is to reduce the preterm birth rate (Holzer et al., 2017).

Kenyon et al followed up 3298 children after 7 years whose mothers participated to the ORACLE I trial. It has been demonstrated that there were no differences between the two groups of the ORACLE I study regarding functional impairment. These finding may underline that using antibiotics in women with PPROM may be relevant and seems not harmful in long-term (S Kenyon et al., 2008).

Moreover, 3196 children whose mothers were part of the ORACLE II trial were also followed-up. On one hand, an increase in children with functional impairment has been found and in another had it has been noted that cerebral palsy was likely to be associated with the treatment with either antibiotics. A greater effect can be expected when both antibiotics have been administrated (S. Kenyon et al., 2008).

Therefore, it has been concluded that the prescription of antibiotics for the treatment of preterm labor seems to be adequate only in the presence of clinical signs of infections.

7. PHYSIOLOGICAL CHANGES IN PREGNANCY MAY INFLUENCE PHARMACOKINETICS

Treatment and dose strategies are based on adult dose most commonly from male or from non-pregnant women. However, in order to achieve therapeutic effects, treatment should be adjusted for pregnant women because several physiological changes may certainly influence pharmacokinetics of xenobiotics. Therefore, potential maternal and fetal risks can be prevented. Regarding the pharmacologic aspect, a drug may exert its therapeutic effects only if a sufficient concentration of the drug reaches the target tissue. Too high concentrations of the drug may cause side effects, whereas too little concentrations are associated with no therapeutic effects at all. Dose regimen and effects are based on pharmacokinetics and the pharmacodynamics respectively. Pharmacodynamics describes what the drug does to the body, whereas pharmacokinetics concerns what the body in turn does to the drug. LADME is an acronym for the essential parts of the pharmacokinetic and it stands for: Liberation, Absorption, Distribution, Metabolism and Excretion. Also, the transport has a particular importance. Drug specific pharmacokinetic properties should be determined in order to improve treatment efficacy and decrease both maternal and fetal risk.

Drug adsorption

The drug can be absorbed after its liberation occurred. This phase is characterized by bioavailability, which is indicated as percentage of active drug. Bioavailability certainly depends on the rout of administration. It is considered to be 100% after intravenous administration. In the contrary, for orally administrated drugs, bioavailability is large altered due to an adsorption across the intestinal epithelium and most importantly due the first pass metabolism. In addition, pH value of the stomach, nutrition, intestinal transit time, intestinal metabolism, adsorption and efflux processes influence largely the bioavailability. Bioavailability depends on the route of administration. Therefore the route should be carefully chosen in order to achieve the desired therapeutic effect. Delays or drug loss can lead to treatment failure. For instance, a delay in time to reach maximal concentration has been noted after intramuscular administration. Further, nausea and vomiting may decrease drug availability and therefore doses should be adjusted in that case. Gastrointestinal variations have also a minimal effect on the amount of the bioactive drug. During pregnancy, an increased gastric pH is due to an increase mucus secretion with a simultaneous

decrease in gastric acid production. These changes result in a reduce absorption of week base such as caffeine and an increase ionization of week acids like aspirin. Progesterone mediates a delay in intestinal motility what in turn results in delayed gastric emptying and increased transit time (Feghali et al., 2015). In pregnancy, the perfusion of the skin is increased and therefore the cutaneous absorption is enhanced. An increased lung function may also influence the absorption of the administrated drug. Due to a hyperventilation, more CO remains in the blood and thus the pH of the blood decreases. Increased cardiac output and intestinal blood flow contribute to an increase drug absorption.

Drug distribution

The distribution volume (Vd) is actually a theoretical volume and an important parameter in pharmacokinetics. It indicates the degree to which an administrated drug is distributed in the tissues in the same concentration that it is observed in the blood plasma. The parameter is expressed in L or in L/kg body weight. A higher Vd can be found for lipophilic drugs and substances with a low rate of ionization, as there are highly distributed into the tissue. Also, in case of liver and kidney failure, higher volume of distribution is also found. On the contrary, hydrophilic drugs or substances with a high protein binding capacity and high molecular weight have a lower Vd because they are more likely to remain in the plasma. This parameter is especially important in order to determinate the loading dose required to reach therapeutically relevant doses. There are several factors including tissue perfusion, lipid solubility and plasma protein binding are primary which influence the distribution of xenobiotics. Essential for the evaluation of the distribution of administrated drug is, that the fetus and the amniotic fluid represent additional compartments. Since the 16^{th} week of gestation, cardiac output increases up to 7 L/min and influence the distribution of the administrated drug. In pregnancy, plasma volume increases by approximately 42 % and thus the plasma proteins are diluted. Blood volume is also increased. Even since the 6^{th} week of gestation an increase has been noted (Pinheiro & Stika, 2020) . Thus, a greater proportion of unbound drugs result which is decisive for the therapeutic effect. Total body water is also increased by 8 L what influences once again the distribution of hydrophilic drug. Extracellular fluid is increased during pregnancy. Maternal body fat increases by 4 kg which leads to a greater Vd for lipophilic drugs. The drug remains longer in the body and therefore a dose adjustment should be considered. Plasma proteins such as albumin and alpha 1-acid glycoprotein are also reduced. Higher concentration of

unbound drugs are found in the plasma. Due to the increase in body mass of approximately 10-15 kg, the distribution of the drug may be altered.

Drug metabolism

Metabolism consists of the chemical modification of the administrated drug. Some drugs are given as prodrug and are actually converted into their active form only by metabolizing in the body. In the contrary, some drugs lose their activity once they have been metabolized. The main organ responsible for the metabolism is the liver. Intestine and placenta also contribute to the clearance of a drug. Clearance is one of most important pharmacokinetic parameters and determinates the elimination of a drug. The total plasma clearance indicates the amount of plasma from which a drug is completely cleared in a unit of time. It represents the sum of the clearances of all organs involved in elimination, primarily the kidneys and the liver. Hepatic blood flow and the extraction ratio determinate the clearance in the liver. The activity of the enzymes involved depends on gender, ethnicity or age. Furthermore, enzyme polymorphism may lead to an altered metabolism. Hepatic metabolism can be classified into two phases. In the first phase, oxidation, reduction or hydrolysis occur in order to make the xenobiotic more hydrophilic. The second phase is characterized by the conjugational reaction, in which glucuronic acid or sulfate are added to the molecule which in turn makes the molecule even more hydrophilic and thus facilitate its excretion into urine or bile. The enzymes belonging to the cytochrome (CYP) P450 family are predominant in the phase I. In pregnancy CYP 2A6, CYP 2D6, CYP 2C9 and CYP 3A4 shown an increased activity. The activity of CYP 1A2 and CYP 2C19 is decreased. This explains that the metabolism of the high active enzymes' substrates is enhanced and therefore the dose should be adjusted. 17-hydroxyprogesterone caproate, which is a well-known drug used to prevent preterm delivery, increases the activity of CYP 2C19. As a consequence, dosage of CYP 2C19 substrates should be increased when 17-hydroxyprogesterone caproate is additionally indicated to the patient. Also, sexual steroids may enhance activity of maternal liver enzymes and thus lead to an accelerated inactivation of drugs. It seems therefore important to mention, that some drugs may induce or inhibit essential CYP enzymes which cause an altered metabolism and thus dosage adjustment is required. The enzymes of the phase II such as UGT1A4 happened to be more active during pregnancy (Feghali et al., 2015)

Also, maternal genotype influences the altered activity of essential enzymes. For instance, it has been found that the variability in a special allele of the CYP 3A5 coding gene causes an altered clearance of nifedipine, a prominent drug used for tocolysis (Haas et al., 2013).

11β-hydroxysteroid dehydrogenase type 2 enzyme is involved in changes of the cortisol concentration. Its role is to convert biological active cortisol into its non-active form, cortisone in order to provide an important increase. It should be noted that betamethasone as well as dexamethasone have a low affinity to this enzyme which results that the two synthetic corticosteroids are barely metabolized by 11β-hydroxysteroid dehydrogenase type 2. Further, at term a decrease of 11β-hydroxysteroid dehydrogenase type 2 enzyme has been noted which explains the greater fetal exposure of glucocorticoids (Bloise & Matthews, 2019). The barrier function of 11β-hydroxy-steroid dehydrogenase type 2 decrease towards the end of gestation in placenta whereas 11β-hydroxy-steroid dehydrogenase type 1 is predominant in decidua, chorion, amnion and in the endothelial cells. This enzyme catalyzes the reduction of cortisone into cortisol in order to increase the activation of the glucocorticoid receptors. A decisively rise of the cortisol level has therefore been found (Schneider et al., 2016).

Drug elimination

The majority of the drugs is eliminated by the kidney and the renal drug excretion depends on the glomerulus filtration rate (GFR). Since the first trimester, GFR is increased by 50% and remains high during pregnancy. This results in turn in renal tubular transport including secretion and reabsorption. Regarding the renal function of the pregnant woman, the glomerulus flow rate is increased and therefore the renal clearance too. Because the renal elimination is enhanced, it is important to adjust the dose for drugs that are mainly excreted through the kidney for pregnant women with renal insufficiency (Feghali et al., 2015).

Drug transport

Drug transporters play a key role in adsorption, distribution, elimination and finally in the effect of a drug. The placenta serves primarily for the exchange of substances between the maternal and fetal blood. The syncytiotrophoblasts which are the functional cells of the placenta mediate the transport. A thin layer of tissue, consisting of vascular endothelium, connective tissue and villi

epithelium, separates the intervillous space from the lumen of the villi capillaries. This is the so-called placenta barrier and regulate the transfer of several molecules and has therefore a protective effect on the fetus. Actually, the placenta villi contribute to an increase of the surface area of diffusion. In one hand, oxygen and nutrients are absorbed by the fetal capillary blood and in another hand, carbon dioxide and other metabolic end products reaches the maternal blood. An additional function of the placenta is the production of hormones that influence the course of pregnancy.

Drugs may reach fetal circulation via passive transport such as paracellular transport, facilitated diffusion and diffusion. The transfer trough diffusion depends mainly on the chemical properties of the drugs. Especially, the lipophilicity, the pH and the grade of ionization has a large impact on the transport. For instance, non-ionic drugs pass the placenta more easily. Also, the lipid membrane of the placenta facilitates the transport of lipophilic substances, such as synthetic corticosteroids, which are used for the acceleration of lung maturation. Additionally, the ability to bind to a transport protein with a high affinity may be restrictive for the passing through the membrane. The molecular weight of the drug is also decisive. Of course, the blood flow from the placenta contributes to a better transportation. In case of facilitated diffusion, molecules cross the membrane via specific transmembrane transporters and follow their concentration gradient. Thus, this process is considered to be passive and therefore it does not directly involve energy from ATP hydrolysis. The transport ends when the system is saturated. Drugs similar to endogenous substances reach fetal circulation via facilitated diffusion. The placenta transfer occurs also via active transport. In this case, energy is required in order to assure the transfer of the molecules against the concentration gradient. Various transporters enable active transport of xenobiotics resembling to endogenous substrates like for instance steroid hormones. The dominant transporters located in the placenta are phosphogycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporter (OAT1). Substrate of P-gp are for instance cortisol or aldosterone and those for BCRP are antibiotics, estrogen and calcium channel blockers. Progesterone may lead to an increased expression of P-pg and BCRP in trophoblast cell lines (Yeboah et al.,2006). Further, an increase of maternal and fetal glucocorticoid is accompanied by a decrease of P-gp. P-glycoprotein is a membrane protein, a so-called ABC transporter and transport its substrates from the cell membrane into the extracellular space by consuming ATP. It is the gene product of the ABCB1 gene and is involved in the development of multidrug resistance. P-pg is active efflux transporter located at the apical surface of the microvillus membrane of the syncytiotrophoblast and prevents the excessive transport of both endogenous substances and xenobiotics. Therefore, it plays a major role in

protecting the fetus from potential toxic substances. It is responsible for the transport of hormones. This transporter is located in the placenta, liver, kidney and in the blood-brain barrier. It has been found that some exogenous substrate may alter the expression of the transporter. Inductors such as betamethasone and dexamethasone have a high affinity for P-pg and therefore enhance the barrier function of transporters and the elimination of drugs. ACS use may alter fetal protection due to its regulatory effects on placental P-pg (Iqbal et al., 2012). The expression of transporters declines with advancing gestation. Due to a reduced expression of this efflux transporter, fetal exposure to ACS will more likely increase in late gestation (Bloise, 2019). In one study, it has been shown that the expression of P-gp was significantly reduced in placentas from infants considered to be small for gestational age. This raises the concerns that the expression of P-pg may have a major role in this case (Hodly et al., 2013).

In pathological pregnancies, alteration of the expression has been noted (Iqbal etal.,2012). Most relevant seems that the expression was also decreased in preterm placentas and in placenta from women with preeclampsia. It has been further suggested that hypoxia may be related to the altered expression of the transporters (Evseenkoet al., 2007).

Transfer through the placenta depends on the chemical properties of the drug.

Furthermore, the different pH value in compartments are decisive of the transport of molecules. A decreased albumin concentration noted in pregnancy contributes to a creation of a gradient and influence the transportation of the drugs to the fetal circulation.

All in all, physiological changes in pregnancy may lead to altered pharmacokinetics of administrated drugs. Generally, it is considered that the concentration of the drugs may be reduced and therefore dosage should be adjusted in order to reach therapeutic plasma levels. This is especially of great importance in case of chronic disease where continuous drug levels are required.

8. CONCLUSION

One of the most important intervention in order to improve the neonatal outcome is the administration of corticosteroids passing the placenta and inducing fetal lung maturation and surfactant synthesis. It is recommended to carry out the administration between 24 weeks of gestation and 34 weeks of gestation. 2x 12 mg betamethasone are administrated within 24 hours in the muscle of the mother. Alternatively, 4 x 6 mg dexamethasone every twelve hours can be used. However, it remains unclear which of the two drugs is preferred. It has been underlined that the treatment with corticosteroids leads to a significant reduction of the incidence of severe complications including RDS, IVH and NEC. Likewise, the risk of perinatal death and neonatal death are reduced. Short-term beneficial effects support the use of a single treatment course in women at risk of imminent preterm birth.

However, this therapy is associated with potential short-term risks such as intrauterine growth restriction, hypoglycemia, altered stress response systems, cardiovascular adverse effects. In fact, hypoglycemia is considered to be associated with developmental delay (Kerstjens et al., 2012). According to recent findings of a population-based retrospective cohort study, it has been found that preterm born children antenatally exposed to corticosteroids have mental and behavioral disorders. Interestingly, this also occurred in children who were exposed to an administration before birth but were born at term. Most importantly it has been found that actually 45,27% of the children were born at term. This percentage is not in accordance with the number collected in clinical trials (5,29%). This indicates that there may be a discrepancy between the selection criteria for clinical studies and those applied in daily clinical practice (Räikkönen et al., 2020). Therefore, it is essential to diagnose preterm birth carefully. The diagnosis should be improved to prevent unnecessary administration of corticosteroids associated with long-term risks. Incorrect evaluation of the symptoms can have a serious influence on the course of the pregnancy and the up-coming treatment of the mother.

All in all, the treatment is considered to be safe and the most beneficial when the administration occurred 1-7 days before birth. Moreover, it should be noted that potential risks change with the gestational age. This should be taken under account for the administration of the drug. The timing of the application is certainly relevant but the “optimal timing” remains unclear. Further, an increased risk of necrotic enterocolitis has been found when the second betamethasone dose has been administrated 12 hours after the initial course. Additionally, repeating the administration is

possible only at persistent risk of preterm birth and should be done 7 days after the initial course and at less than 29 + 0 weeks of gestation. It has been pointed out that, neither the choice of the drug nor the treatment schedule has been optimized even though there are still concerns about the excessive fetal exposure of corticosteroids which may be harmful. It has been supposed that excessive exposure to corticosteroids may lead to these side effects, which may be involved in programming for adult diseases such as hypertension, insulin resistance, diabetes mellitus and metabolic syndrome (Benediksson 1993; Dalziel 2005, Newnham 1999.)

It is therefore necessary to find an adequate dosing in order to insure in one hand the lung maturation and in another hand to limit the potential risks. The main issue is that the pharmacokinetics were not systematically evaluated yet to establish optimal drug choice, dose and treatments. Due to physiological changes in pregnancy it remains necessary to evaluate the pharmacokinetics in patients in order to improve the therapy. It would be necessary to conduct further studies to optimize the dosage and route.

It has been supposed that different fetal growth responses may be primary related to the duration of the exposure. By the direct administration in the muscle of the fetus, a reduced exposure has been achieved. However, there are no current studies performed yet comparing direct injection into the fetus to maternal intramuscular administration. It is therefore necessary to perform randomized controlled trials focusing and the related harms or benefits of the different routes. It is still recommended to stay with the current standards due to a lack of good quality data on health outcome regarding the direct fetal injection of betamethasone.

This therapy is conducted in high income countries. Further studies are necessary to evaluate the therapy in low income countries.

However, these findings concern singleton pregnancies. Unfortunately, there is a lack of evidence in multiple pregnancies. It seems therefore necessary to evaluate closely the use of antenatal corticosteroids in multiple pregnancies. The performance of a tocolysis is also considered as a major tertiary prevention measurement. Nifedipine, indomethacin and atosiban are preferably used for tocolysis. These tocolytic agents lead to a prolongation of the pregnancy for 48h which allows the full application of corticosteroids. Also, time is gained for the transfer to a neonatal care center. Magnesium sulfate is not suitable as tocolytic agent and it moreover used for neuroprotection. Antibiotics are only indicated in women with PPROM and in suspected intrauterine infections. Because of low permeability of macrolide antibiotics (Witt et al., 2003) future investigations should focus on different antibiotics like clarithromycin. It should be well recognized that in the situation

of unruptured membranes administration of antibiotics leads to a significant of cerebral palsy in contrast to placebo administration. As shown in the text there is still a considerable lack of knowledge concerning the fundamental causes and pathways of preterm birth. A lot of clinical research projects are underway by looking at the database of the platform for registered clinical trials – clinicaltrials.gov. Entering the search term “preterm birth” reveals 680 clinical trials actively recruiting patients. 15 of these studies focus on antenatal steroids and 8 studies are shown in this platform to deal with tocolysis in context of preterm birth.

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10. ABSTRACT

10.1. GERMAN

Frühgeburten sind mit Komplikationen des Neugeborenen wie Atemnotsyndrom, Intraventrikuläre Blutung und Nekrotisierende Enterokolitis sowie einer erhöhten Mortalität verbunden.
Deswegen versucht man mit präventiven Maßnahmen die Frühgeburt bestmöglich zu verhindern oder deren pathologische Konsequenzen zu reduzieren. Diese Präventionsmaßnahmen können in Primäre, Sekundäre und Tertiäre eingegliedert werden.
Ziel dieser Diplomarbeit ist es, die verschiedenen eingesetzten Medikamente im Rahmen einer drohenden Frühgeburt zu präsentieren. Im Focus steht die Gabe der Glukokortikoide im Rahmen einer Induktion der Lungenreifung. Zum Einsatz kommen die synthetischen Glukokortikoide Betamethasone und Dexamethasone, die Aufgrund ihrer Planzentagängigkeit ausgewählt werden. Es werden 2x 12mg Betamethason im Abstand von 24h i.m. verabreicht. Alternativ, werden 4x 6 mg alle 12h Dexamethason gegeben. Das Timing der Applikation ist durchaus zu berücksichtigen. Es wird empfohlen die Therapie zwischen 24-34 Schwangerschaftswochen durchzuführen. Zu betonen ist, dass das „optimale Timing“ bislang noch unklar ist. Ausschlaggebend ist, dass die antenatale Gabe von Glukokortikoiden zu einer Reduktion der neonatalen Komplikationen führte und auch die kindliche Mortalitätsrate sank. Die Vorteile, die die Behandlung mit sich bringen, überwiegen den Risiken. Die Gabe von den Glukokortikoiden wird als Standardtherapie für Patienten bei drohender Frühgeburt gesehen.
Darüber hinaus ist es aus pharmazeutischer Sicht interessant, die Applikation genauer zu betrachten. Die Dosierung wurde seit 1972 nicht geändert und es fehlen Daten von pharmakokinetischen Studien, die notwendig wären, um die Applikation zu verbessern.
Durch die Verabreichung der Glukokortikoide direkt in die Muskulatur des Fötus war die Dauer der fötalen Glukokortikoid-Exposition kürzer und der alternative Weg ist mit einer Verringerung der möglichen Nebenwirkungen verbunden. Dies wurde in einem Tierexperiment gezeigt.
Weitere Medikamente kommen als Tokolytikum zum Einsatz im Rahmen der Frühgeburt. Diese können die Schwangerschaft über 48h hinauszögern, um eine vollständige Behandlung mit Glucokortikoiden zu gewährleisten und den Transport zu einer neonatologischen Intensivstation sicherzustellen. Hoch dosiertes Magnesium-sulfat wird zur Neuroprotektion eingesetzt. Applikation von Antibiotika kommen nur im Falle eines frühen vorzeitigen Blasensprungs oder bei nachgewiesener Infektion im Bereich der Geburtswege in Frage.

10.1. ENGLISH

Preterm births are associated with neonatal complications such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC).

Therefore, preventive measures are taken to avoid premature birth as much as possible. These can be divided into primary, secondary and tertiary.

The aim of this diploma thesis is to present the different drugs used in the context of an imminent premature birth. The focus is on antenatal corticosteroid treatment in the context of induction of lung maturation. Synthetic glucocorticoids, betamethasone and dexamethasone are used, which are selected on the basis of their ability to cross the placenta. 2x 12mg betamethasone are administered i.m at 24 h interval. Alternatively, 4x 6 mg dexamethasone are given every 12 h. The timing of the application must be taken into account. It is recommended to carry out the therapy between 24-34 weeks of pregnancy. It should be emphasized that the "optimal timing" is still unclear. The decisive factor is that the glucocorticoids led to a reduction in neonatal complications and also reduced the mortality rate. The benefits of the treatment outweigh the risks. The administration of glucocorticoids is seen as the standard therapy for patients at risk of preterm birth.

In addition, from a pharmaceutical point of view it is interesting to take a closer look at the application. The dosage has not been changed since 1972 and there is a lack of data from pharmacokinetic studies that would be necessary to improve the application.

By administering the glucocorticoids directly into the muscle of the fetus, the duration of the fetal exposure of glucocorticoids was shorter and the alternative route is associated with a reduction in potential side effects. This has been shown in an animal study.

Other drugs are used as tocolytics in preterm delivery. These achieve to delay the pregnancy beyond 48h to ensure complete treatment with glucocorticoids and also to ensure transport to a neonatal intensive care unit. Magnesium sulphates are used for neuroprotection. Antibiotics can only be used in the case of PPROM.