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Continuous glucose monitoring (CGM) in preterm newborn: the effects of antenatal corticosteroids prophylaxis for lung maturation

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ABSTRACT

Background: A correlation between antenatal corticosteroid (ACS) administration for lung maturation and neonatal hypoglycemia has been recently demonstrated in late preterm newborns.

Aims: The aim of this study was to evaluate glycemic control through continuous glycemic monitoring (CGM) in preterm infants born to mothers who received corticosteroids prophylaxis during pregnancy to induce lung maturation. Secondary, we wanted to assess whether there are differences in glycemic trends according to the time elapsed between prophylaxis administration and date of delivery or according to gestational age (≥34 or < 34 weeks of gestation).

Material and methods: a prospective single-center cohort study was conducted in a Tertiary University Unit. All inborn and outborn babies delivered between 31+0 and 34+6 of gestation from February to August 2023 were considered eligible for the study purpose. Antenatal steroid exposition (complete, incomplete, not administered) and timing (distance between steroid and birth) were evaluated. All the neonates included underwent continuous glycemic monitoring in the first 48 h of life.

Hypoglycemia, hyperglycemia, and glycemic variability (expressed by MAGE = Mean Amplitude of Glycemic Excursions) in the first 48 h of life were assessed.

Results: 37 newborns met the inclusion criteria: 26 underwent complete ACS administration, 6 received incomplete prophylaxis, 5 were not exposed. We found a higher number of hypoglycemic events during the first day of monitoring in infants exposed to complete ACS (p= 0,0001). MAGE did not show statistically significant differences between

groups, but it described a higher glycemic variability in newborns exposed to complete ACS. Infants exposed to ACS within 7 days of birth had a higher number of hypoglycemic events (p= 0,0001). In the population exposed to complete ACS, hypoglycemic and hyperglycemic events were more common in newborns born < 34 weeks of gestation (p= 0,05 and p=0,01).

Conclusion: complete ACS administration may increase hypoglycemic events in preterm newborns in the first 24 h of life, especially if administered within 7 days from birth. Therefore, strict glucose monitoring is recommended for all preterm infants (both < 34 and late preterm) with a history of ACS exposure. The CGM could be a useful instrument to check not only hypoglycemic and hyperglycemic events but also glycemic variability.

ABBREVIATIONS

PPROM= Preterm premature rupture of the membranes

RDS= Respiratory distress syndrome

CPAP= Continuous positive airway pressure

ACS= Antenatal corticosteroids

FRC= Functional residual capacity

NCPAP= Nasal continuous positive airway pressure

IVH= Intraventricular hemorrhage

NEC= Necrotizing enterocolitis

AAP= American Academy of Pediatrics

ACOG= American College of Obstetricians and Gynecologists

ALPS= Antenatal late preterm steroids

MFMU= Maternal-Fetal Medicine Units

RCOG= Royal College of Obstetricians and Gynecologists

SIMP= Società italiana di medicina perinatale

LGA= Large for gestational age

PDA= Patent ductus arteriosus

ROP= Retinopathy of prematurity

CGM= Continuous glycemic monitoring

SD= Standard deviation

GV= Glycemic variability

MAGE= Mean amplitude of glycemic excursions

MAG= Mean absolute glucose

NICU= Neonatal intensive care unit

INTRODUCTION

Preterm birth is defined as birth occurring before 37 completed weeks of gestation.

Obstetric conditions that lead to preterm birth include labor induction or caesarean delivery for maternal or fetal indications; spontaneous preterm labor with intact membranes and preterm premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by cesarean section [1].

Worldwide, 11.1% of infants are born preterm every year [2]. Preterm births account for 75% of perinatal mortality and more than half of long-term morbidity. Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications [1]. Preterm babies can be subdivided based on the gestational age at delivery into extremely preterm (<28 weeks), very preterm (28–<32 weeks), moderately preterm (32–<34 weeks) and late preterm (34–<37 weeks) [3]. This subcategorization is important because the gestational age at birth is inversely associated with increased mortality, morbidity and the intensity of neonatal care required at birth [4].

1. RESPIRATORY DISTRESS SYNDROME (RDS)

Respiratory distress syndrome (RDS) is the major cause of respiratory failure in preterm infants; the incidence of the disease is inversely proportional to gestational age and the disease occurs in almost all preterm newborns between 23 and 28 weeks of gestation[5]. This is because preterm delivery interrupts lung maturation in utero resulting in functional and structural reduction of lung capacity and surfactant production.

1.1. Normal development of lung

The growth and development of the lung from conception to birth is divided into five characteristic periods: embryonic, pseudoglandular, canalicular, saccular and alveolar.

The embryonic period (weeks 0 to 6) is the period of organ development or organogenesis. It consists of the development of the respiratory diverticulum, or laryngotracheal bud, up to the origin of the two lung buds with the development of the right and left main bronchi. In this phase the pulmonary arteries bud off 6^{th} aortic arches and the pulmonary vein appears.

The pseudoglandular period (weeks 7 to 16) consists of the development of the complete branching structure of the bronchial tree; by the late pseudo glandular period the airway branching reaches the level of acinus. In this period the vascular development is completed. Moreover, the cellular differentiation of the conducting airways commences and by the end of 12 weeks of gestation cartilage, muscle cells and mucous glands are present in the trachea and segmental bronchi[6].

The canalicular period (weeks 16 to 24) is characterized by the early development of the pulmonary parenchyma, the appearance of the distal acinar unit, and the multiplication of capillaries. In this phase, alveolar epithelial cell differentiation starts with the formation of type I and type II epithelial cells. Type II alveolar epithelial cells are crucial for normal lung development because they are precursors of surfactant production and secretion [6].

The beginning of the saccular period (weeks 24 to 36) represents the current limit of viability for premature birth. At the beginning of this period, the airways end in clusters of thin-walled terminal saccules[6]. These saccules produce, by term, the last generations of airways, alveolar ducts and at the periphery the alveolar sacs [7].

True alveoli can be observed at 32 weeks, and they become more recognizable at 36 weeks. Surfactant synthesis begins in the lamellar bodies contained in the type II alveolar cells. In addition, vascular expansion is characteristic of this phase as blood vessels grow in length and diameter.

In the alveolar phase, which starts after 36 weeks of gestation, true alveoli appear, and the surfactant system matures. Alveolar development continues after birth, and it is considered that the alveolarization is likely to be completed by 18 to 24 months of age, with most alveolar formation completed by approximately 6 months[6].

1.2. Surfactant system

Surfactant system is crucial for maintaining the functional integrity of alveoli.

The surfactant is a protein-phospholipid mixture: the lipid component constitutes about 90% by weight of surfactant and includes phospholipids and neutral lipids, primarily cholesterol. The protein component of pulmonary surfactant represents about 10% by weight, and four surfactant proteins have been described. These are surfactant protein-A (SP-A), SP-B, SP-C and SP-D [8]

Both lipids and proteins are synthesized in alveolar Type II cells and packaged into lamellar bodies (this process starts around 24 weeks of gestation); around 30 weeks of gestation the surfactant start to be released into the alveolar lumen via exocytosis [5].

The main function of the pulmonary surfactant system is to reduce the surface tension at the air–liquid interface. Because of their polar nature, the water molecules at an air–liquid interface experience a greater force of attraction to the other water molecules in the bulk phase, than to the air above, creating a high surface tension[9]. Therefore, with water molecules alone in the alveoli the surface tension would be so high that lung collapse could

occur. The surfactant lipids coat the thin layer of fluid that remains in the lungs after the majority is reabsorbed at the first breath, providing the alveoli with stability, reducing the work of breathing, and preventing alveolar collapse (figure 1)[6].

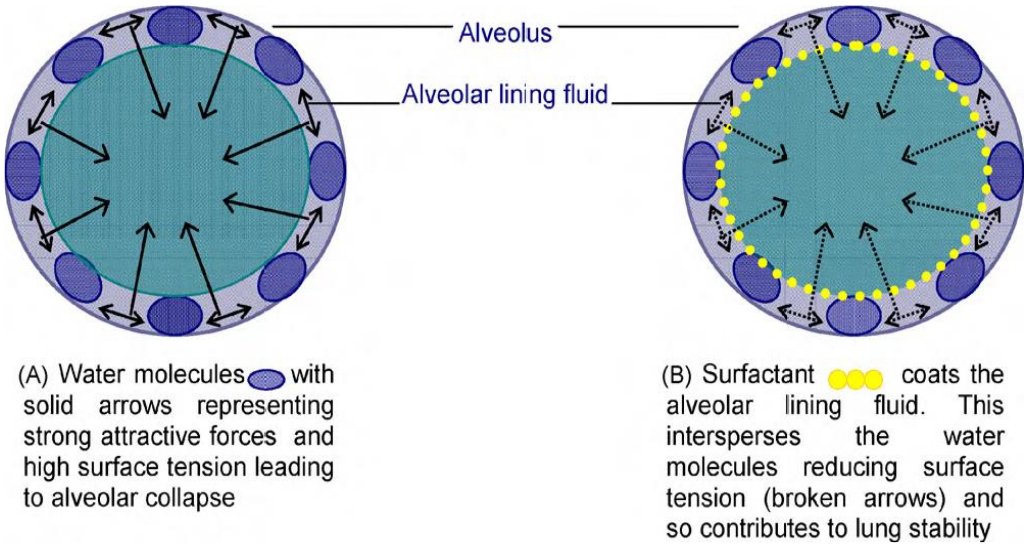

Figure 1: Surfactant coats the alveolar lining fluid reducing surface tension; cited by Normal Development of the Lung and Premature Birth

The other main function of the pulmonary surfactant relates to its role in the innate pulmonary host defense system, which is achieved by hydrophilic surfactant proteins, SP-A and SP-D [9]. These proteins are capable of recognizing, inhibiting and inactivating a broad spectrum of foreign pathogens, making them important effector molecules of the innate immune system [8].

1.3. Cortisol system

Also the cortisol system plays an important role in the maturation of the respiratory system; during the late saccular stage there is a natural increase in fetal concentrations of circulating cortisol that facilitates the final maturation of the fetal lung and stimulates surfactant synthesis. Cortisol also promotes lung maturation by affecting structural changes

in the developing lung, stimulating lung cell proliferation, differentiation of type II alveolar epithelial cells, and thinning of alveolar walls [10].

In a preterm infant, born before 37 weeks of gestation, lung development is within the saccular period, therefore, alveolar maturation is yet to occur, and the capillary network is underdeveloped. Moreover, the surfactant and the cortisol systems are not completely functional. Insufficient surfactant production and secretion results in higher alveolar surface tension, leading to atelectasis and impaired gas exchange [5]. As a result, preterm infants often develop respiratory distress syndrome.

1.4. Risk factors for RDS

In addition to prematurity, male sex and Caucasian ethnicity are risk factors associated with RDS [11]. Sex differences may be due to androgen inhibition of surfactant phospholipid production in males [12] and estrogen acceleration of lung maturation and surfactant production in females [13]. The mechanism underlying the racial disparity in RDS is still not clear, but it could be due to the presence of protective genetic polymorphisms. Also, maternal diabetes may increase RDS risk by leading to fetal hyperglycemia and hyperinsulinism, which decrease the synthesis and secretion of surfactant from alveolar Type II cells [14] [12]. Finally, the elective delivery in the absence of labor, which increases maternal endogenous steroids production, is considered a risk factors for RDS development [15].

1.5. Clinical presentation of RDS

The clinical presentation of RDS begins immediately after birth or during the first hours of life. Marked respiratory distress with tachypnea, subcostal and intercostal retractions, nasal flaring and grunting are the typical presenting signs.

Mild cases may respond to the distending pressures of CPAP and low oxygen concentration, but more severe cases may progress to respiratory failure requiring intubation, mechanical ventilation and administration of exogenous surfactant into the lungs [12] [5], [16] .

In RDS, blood gas analysis shows a picture of hypoxemia and hypercapnia, and the chest radiograph shows reduced lung volumes and an air bronchogram surrounded by microatelectasis and a symmetric, reticulogranular pattern in the peripheral lung fields, with the characteristic appearance of “ground glass” (figure 2) [5].

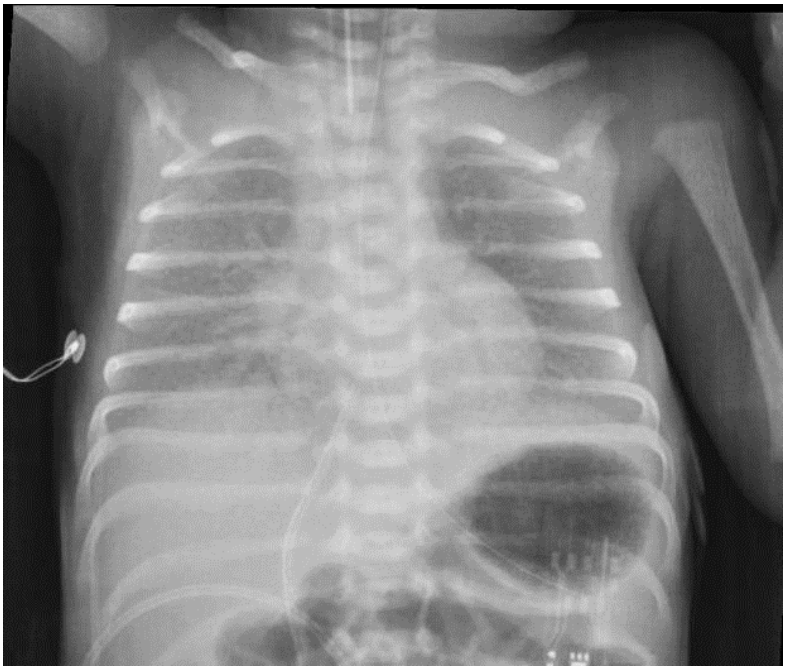

Figure 2: chest radiography showing a typical picture of RDS

1.6. Prevention and treatment of RDS

The observation that some maternal hormones, in particular glucocorticoids, increase lung maturation, is the basis of RDS prevention.

This prevention is carried out by the administration of antenatal corticosteroids (ACS) at high levels to the mother to accelerate fetal lung maturation and increase the activity of enzymes responsible for surfactant biosynthesis. Many clinical trials have demonstrated the effectiveness of the treatment in the prevention of RDS and neonatal mortality [17], [18], and current guidelines recommend a single course of antenatal corticosteroids to all pregnant women between 24 and 34 weeks of gestation at risk of preterm delivery. The steroid used can be betamethasone in 2 doses or dexamethasone in 4 doses. Administration is carried out over 24 hours [19].

Appropriate treatment of neonatal RDS requires optimal respiratory support to create and maintain functional residual capacity (FRC), which is the volume remaining in the lungs after normal, passive exhalation.

Noninvasive ventilation is a common treatment for preterm infants with RDS. It helps to avoid intubation, or provides post-extubation respiratory support, minimizing ventilator-induced lung injury and improving respiratory outcome[20].

The application of nasal CPAP (NCPAP), through nasal cannulas, nasal mask or face mask, delivers a constant positive pressure that consents to recruit the collapsed alveoli and reduce the airway resistance, maintaining the patency of the alveoli despite the absence or reduction of surfactant [12], [20].

CPAP support is initiated using a pressure of 5 or 6 cmH20, which is modified based on the chest X-ray (with the goal of achieving lung expansion of 8 or 9 ventilated spaces). When

an optimal FRC is reached, there should be progressive clinical improvement with normalization of respiratory dynamics and a gradual reduction in oxygen requirements.

CPAP treatment is considered to have failed when, despite adequate pressures, the oxygen demand increases, respiratory acidosis develops, or there is a worsening in respiratory distress.

Caffeine is a drug used in preterm newborns to treat or prevent apnea of prematurity [21]; it acts as an antagonist of adenosine receptors [22], a neurotransmitter that can cause respiratory depression. Its use in preterm infants promotes the success of CPAP in in treating RDS.

Surfactant replacement is considered to be an effective and safe therapy in RDS management by the early 1990s [23]. Systematic reviews have confirmed that surfactant administration in preterm infants with RDS reduces mortality, decreases the incidence of pulmonary air leak (pneumothoraxes and pulmonary interstitial emphysema), and reduces the risk of chronic lung disease at 28 days of age [24], [25].

Many trials have indicated that prophylactic or early surfactant administration, before symptoms develop, has a better outcome [26]. However, more recent randomized clinical trials indicate that the benefits of prophylactic surfactant are no longer evident in infants in whom CPAP support is used routinely [23].

The surfactants currently used in clinical practice today are of animal origin and are enriched with the addition of phospholipids. The surfactant must be delivered directly into the trachea through an endotracheal tube, which can subsequently remain in place to continue mechanical ventilation or be quickly removed with subsequent transition to CPAP support.

The first dose of surfactant should be given early in the course of the disease, and it should be administered to reach a phospholipid dose of at least 100 mg/kg [12]. The following doses of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement; there should be an interval of at least six hours between one administration and the next. Other problems, such as air leak, should have been excluded before repeating the administration [27].

In newborns who fail CPAP support, mechanical ventilation is initiated, with the aim of achieving an adequate FRC and consequently reducing the oxygen requirement.

1.7. Outcome of RDS

The outcome of neonates with RDS has improved in recent years, because of the widespread use of prenatal corticosteroids administration, early use of CPAP support and treatment with exogenous surfactant [5].

Typically, in newborns over 32 weeks of gestation, RDS resolves completely and without pulmonary sequelae; newborns born at earlier gestational ages are at risk of developing chronic lung disease.

2. ANTENATAL CORTICOSTEROIDS

The administration of antenatal corticosteroids (ACS) to women at risk of preterm birth has proven over the years to be one of the most effective practices to reduce the mortality associated with neonatal respiratory distress syndrome.

As previously explained, the utilization of ACS is based on the observation of high corticosteroid levels during the late saccular phase of fetal lung maturation in utero.

In 1969, Liggins observed that premature lambs exposed to antenatal corticosteroids in utero survived longer than control lambs; later in 1972 he conducted the first randomized placebo- controlled study on the administration of betamethasone in women at risk for preterm delivery and found a statistically significant reduction in the frequency of respiratory distress and neonatal mortality among preterm babies born from mothers who had received corticosteroid therapy compared with those born from mothers who had received placebo [17], [28].

Since these classic studies, several further investigations suggested that antenatal steroids reduced neonatal morbidity, and in 1990 the first structured review on corticosteroids was published [17]; this review not only confirmed the effectiveness of the treatment in the prevention of RDS and reduction of neonatal mortality, but also recognized a reduction in the risk of intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) in preterm newborns who had been exposed to ACS [18].

In 1994 the National Institute of Health Consensus Statement affirmed that prenatal corticosteroid therapy reduces mortality, RDS and cerebral hemorrhage in preterm infants born between the 24^{th} and 34^{th} week of gestation [29]. In the Cochrane revision by Roberts of 2006 on the administration of ACS, which included 21 studies, it is concluded that treatment with a single course of antenatal corticosteroids reduces RDS and fewer common serious neurological and abdominal problems, such as cerebroventricular hemorrhage and necrotizing enterocolitis. It also showed that there are no negative effects of the corticosteroid on the mother [18].

According to the American College of Obstetricians and Gynecologists' guidelines (ACOG), treatment with prenatal steroids is recommended to all women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days, including those women with ruptured membranes and multiple gestations [19]. The indications for the use of steroids for women at risk of extremely preterm birth are not yet detailed, because of limited study data. A meta-analysis showed no benefits on neonatal mortality and morbidity before 26 weeks gestation[30], conversely other investigations have indicated improved survival in extremely preterm infants [31] and a lower rate of death and neurodevelopmental impairment at 18-22 months, after ACS administration [32].

Therefore, at present, the decision regarding the prophylaxis before the 24th week should be based on a family's opinion regarding resuscitation, independent of membrane rupture status and fetal number [19].

In addition, with regards to late preterm newborns (between 34 and 37 weeks of gestation), the role of steroid prophylaxis is controversial.

The Antenatal Late Preterm Steroids (ALPS) trial, a double-blind placebo-controlled study, conducted in 17 Maternal-Fetal Medicine Units (MFMUs) of the United States concluded that the steroids administration significantly reduces the risk of RDS in late preterm newborns, but determines a significant increase in neonatal hypoglycemia, without modifying the incidence of other maternal and fetal complications [33]; conversely in the meta-analysis by Roberts and Daziel, RDS decreased when steroids were administered by 33 up to 34+6 weeks, but there were no significant differences if the steroids were administered from 35 to 36+6 weeks of gestation [18].

At present, the Royal College of Obstetricians and Gynecologists (RCOG) recommends a single course of corticosteroids for women who are at risk of preterm delivery up to 34+6 weeks [34], while the Society for Fetal Maternal Medicine and the ACOG suggest prophylaxis with prenatal steroids between 34 and 36+ 6 weeks in case of risk of preterm birth within seven days and in any case in women who have not received a previous course of steroids[19] [35].

The use of ACS is also recommended in women with pPROM and is not contraindicated in women with subclinical or clinical chorioamnionitis, as long as it does not postpone delivery and with concomitant broad-spectrum antibiotic therapy.

Prophylaxis is performed by administering two doses of 12 mg intramuscular betamethasone every 24 or 4 doses of 6 mg intramuscular dexamethasone every 12 hours [19]. Limited and inconsistent data are currently available to recommend one corticosteroid regimen over the other [36]. Because treatment with corticosteroids for less than 24 hours is still associated with significant reduction in morbidity and mortality, a first dose of corticosteroids is also recommended if the possibility of administering the second dose is unlikely, based on the clinical scenario [37].

The benefits of ACS begin after 24 hours from administration and last up to 7 days, but debate still exists whether the benefits of ACS administration persist after these 7 days; remote ACS (administrated more than 7 days before the delivery) seems not to reduce the RDS development but could decrease its severity [38].

This is an important question still not completely solved, because if the benefits of ACS last beyond 7 days, then the administration of a second course of ACS would not be necessary. On the other hand, if the positive effects are temporary, then additional doses of steroids

should be considered for those women who do not deliver within 7 days after the initial treatment. In addition, several studies have shown that repeat prenatal corticosteroids reduce neonatal respiratory complications of prematurity, but adverse outcomes have been reported concerning cognitive development [39] and reduction in birth weight [40].

The 2015 Crowther Cochrane meta-analysis included 10 trials with a repeat course of corticosteroids and confirmed a positive effect on respiratory distress development and an association with small reduction in size at birth, without other significant adverse outcomes in early childhood [41]. The 2022 Cochrane update determined that current available evidence showed no significant harm to mothers and infants in early childhood after receiving repeated doses of ACS but concluded that further research is needed to understand the long-term outcome [42].

So, at present, the ACOG's indication suggests that a single repeat course of antenatal corticosteroids should be considered in women who are less than 34 weeks of gestation and are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously[19]. According to the SIMP (Società italiana di medicina perinatale), multiple doses are recommended when the first cycle is given before 26 weeks or when a real threat of preterm birth is present before 33 weeks[43].

If concern regarding short- and long-term side effects on newborns after repeat course of steroids have been expressed, a single course of ACS is considered to be safe. With regard to adverse effects, hypoglycemia in late preterm infants has been described after ACS administration [33], [44], [45].

As far as mothers are concerned, it seems not to be a significant increased risk of infection after steroid administration [46]; instead, the effect of corticosteroids on increasing maternal glycemia is known, but NICE guidelines recommend that not even maternal diabetes should be considered a contraindication to the administration of ACS[34], [47].

3. GLYCEMIC CONTROL

3.1. Hypoglycemia

Hypoglycemia in the neonatal period is one of the most common metabolic problems; however, its definition is controversial because of the difficulty in correlating glycemic values with clinical symptoms [12].

The most common definition of hypoglycemia is a blood glucose concentration of less than 47 mg/dL (2.6 mmol/L), but according to the American Academy of Pediatrics, hypoglycemia is defined as glucose <40 mg/dL in the first 4 hours of life or <45 mg/dL 4–24 hours of life; treatment intervention is recommended at glucose <25 mg/dL in the first 4 hours of life or <35 mg/dL between 4 and 24 hours of life [48].

Instead, the Pediatric Endocrine Society affirms that in babies at risk of hypoglycemia, glucose concentrations should be > 50 mg/dL (2.8 mmol/L), or > 60 mg/dL (3.3 mmol/L) if interventions beyond normal feeds are required [49].

Glucose is the primary source of energy for fetal growth. During pregnancy, almost all the fetal glucose is supplied by the maternal circulation via transplacental diffusion [50], dependent on the maternal-fetal concentration gradient, which allows fetal glucose levels to remain at about 2/3 of maternal glucose levels [51], [52]. After birth, at the moment of

cord clamping, there is an abrupt interruption of maternal oxygen and nutrient support, and the newborn must start to provide for its own glucose homeostasis. To do that it initiates glycogenolysis from liver reserves, triggers gluconeogenesis, and uses nutrients that come from feeding [12].

During this transition, blood glucose drops rapidly in the first two hours of life and then rises again at about three hours of life, due to the activation of hepatic glycogenolysis, which is the fastest mechanism activated. The high rate of glycogenolysis leads to depletion of hepatic glycogen stores, especially and more rapidly in preterm infants in which liver glycogen deposits are limited [53].

Gluconeogenesis is not immediately effective due to the initial low enzymatic activity of this metabolic pathway; it starts after some hours from birth and reaches its maturation after 12 hours [50].

Glucose oxidation provides about 70% of the brain's energy demand, while the remaining 30% is provided by ketone bodies and lactate, which are important to reduce the glucose requirement; these alternative fuels are produced through hepatic ketogenesis in the first hours of life in term babies. Conversely, in preterm infants this metabolic pathway is very limited due to the lack of adipose tissue accumulation [54].

Hypoglycemia develops in newborns with low glycogen and fat stores, with limited capacity to generate glucose via the gluconeogenesis pathway or with excessive peripheral tissue utilization of glucose, like in an infant of a mother with insulin dependent diabetes or a large for gestational age newborn (LGA) [55].

Several studies have shown that preterm infants are at a greater risk of developing hypoglycemia in the first week of life than term infants. Predisposition to hypoglycemia

could be due to many factors such as an increased basal metabolism of glucose, lower capacity for production of alternative energy sources and presence of associated clinical conditions, such as perinatal asphyxia, hypoxia, sepsis, and hypothermia [53].

The effect of mild transient asymptomatic hypoglycemia on the brain is currently unclear. On the other hand, prolonged neonatal hypoglycemia has been associated with various forms of neurological impairment, such as developmental delay, seizures, visual processing problems, and cognitive difficulties [53]. Nevertheless, many issues regarding which patients are at risk, about outcome and follow-up options remain unanswered. A recent meta-analysis, considering neurodevelopmental outcomes after neonatal hypoglycemia, found a correlation between hypoglycemic events and an increased risk of visual motor impairment and executive dysfunction in early childhood and an increased risk of literacy and numeracy problems in later childhood. However, the authors underlined the need for additional studies to determine long-term outcomes in neonates at risk [56].

3.2. Hyperglycemia

Preterm infants not only have an increased risk of developing hypoglycemia but also of developing hyperglycemia and generally a condition of glycemic instability. Hyperglycemia is defined as blood glucose levels greater than 180 mg/dl (10 mmol/L).

Factor risks to develop hyperglycemia are low birth weight, low gestational age, septicemia, treatment with corticosteroids and intravenous glucose infusions given at rates exceeding normal infant glucose turnover rates (~6 mg/kg per minute) [57].

If in sick patients (both preterm and term newborns) hyperglycemia is an effect of stress and increased levels of catecholamines, which are known to induce glucose metabolism, the glucose intolerance observed in otherwise healthy, premature infants has a complex

pathogenesis: low levels of postnatal insulin and the small mass of insulin-dependent tissue (primarily muscle and fat) determine intracellular glucose deprivation, that may start counterregulatory responses and catabolism, leading to hyperglycemia [58].

Hyperglycemia can lead to acute problems of osmotic diuresis and metabolic acidosis, and it has also been associated with increased risk of other complications such as IVH, NEC, patent ductus arteriosus (PDA) and retinopathy of prematurity (ROP) [59]. Consequently, therapeutic changes and glycemic rate changes in the first days of life are extremely important for maintaining normoglycemia and avoiding complications related to hypoglycemia and hyperglycemia.

3.3. Clinical manifestation of hypoglycemia and hyperglycemia

In newborns, signs of hypoglycemia are often blurred or completely absent. Whether they occur are adrenergic and are given by activation of the autonomic nervous system in response to neuroglycopenia.

They include sweating, pallor, apneic episodes, tachypnoea, thermal instability, hypotonia, poor feeding, abnormal cry (weak or high- pitched), irritability, diaphoresis, tremors, jitteriness, exaggerated Moro reflex, lethargy and seizures [60]. These signs are not specific to hypoglycemia and can also be manifestations of other neonatal disorders (septicemia, congenital heart disease, ventricular hemorrhage and respiratory distress syndrome).

Also, neonatal hyperglycemia is mostly asymptomatic; possible symptoms include dehydration due to osmotic diuresis, weight loss, failure to thrive, glucosuria, ketosis and metabolic acidosis.

3.4. CGM: continuous glucose monitoring

Strict monitoring of glucose levels is necessary to prevent and treat glucose instability in newborns. This is routinely achieved by serial blood glucose monitoring by heel lancing; however, this method has some limitations. First, it is an invasive procedure, with potential adverse effects on neurodevelopment. Moreover, low glucose concentration may not be detected by intermittent samples, and blood glucose concentration may be assessed during a temporary hyperglycemic or hypoglycemic episode, leading to unnecessary treatment [61]. Recently, continuous glucose monitoring systems (CGM) have been used for the management of diabetes mellitus in adults and children; it has the advantage of tracking glucose levels continuously, providing a reliable glycemic profile of patients. This monitoring can lead to improved metabolic control and possibly to better long-term outcomes. Nevertheless, its use in neonatal intensive care is still controversial [62]; that because the clinical interpretation of CGM is challenging as it needs to be interpreted as a dynamic and integrated value. In addition, in the absence of well-established guidelines, there is a risk that CGM could lead to unnecessary or even harmful interventions [61]. CGM devices measure glucose concentration in the interstitial fluids, through subcutaneous or transdermal sensors. Among the subcutaneous, there are microdialysis fibers and amperometric needle electrodes; the latter are commercial devices currently used in newborns. These consist of a fine needle sensor connected to a non-implantable transmitter that powers the sensor and sends raw data to a monitor, either by cable or Bluetooth. The system displays the resulting output in “real time” on the monitor. Amperometric sensors measure the current flowing from an oxidation (electron producing) reaction at a working electrode to a reduction (electron consuming) reaction at a counter

electrode. The working electrode is coated with glucose oxidase which catalyzes the oxidation of glucose when a voltage is applied, resulting in transfer of electrons to a chemical mediator, usually hydrogen peroxide. A reference electrode is used to ensure a stable voltage applied to the working electrode, but reference and counter electrodes are often combined. In addition, subcutaneous sensors require a barrier membrane to limit glucose access to the sensor because of the oxygen deficiency in the subcutaneous environment relative to glucose supply. Each manufacturer has their own proprietary method for combining these elements within the needle sensor [61].

Raw signal data from the electrode is generated almost every 10 seconds and is elaborated to give a glucose value every 5 minutes, thus providing near continuous measurement [61]. Blood glucose concentration is estimated from this signal using proprietary algorithms based on regular calibration to blood glucose measurements (minimum 12 hourly).

3.5. Glycemic variability

In addition to hypoglycemia and hyperglycemia, a third glucose measurement called glycemic variability (GV), which includes both upward and downward acute glucose changes, has attracted interest in recent years. It has been shown that increased glycemic variability is associated with oxidative stress, which results in direct cellular damage and apoptosis [63]. It is of great interest because in preterm infants, oxidative stress plays a major role in the pathogenesis of many neonatal diseases, including periventricular leukomalacia, bronchopulmonary dysplasia, and retinopathy of prematurity [64].

GV is a complex phenomenon that includes both intraday and interday variability. The intraday component comprises vertical glycemic fluctuations throughout the day. The interday component is defined as day-to-day glucose variation.

Calculating standard deviation (SD) around a mean glucose value measured over a 24 hours period using CGM is probably the most appropriate method to assess intraday glycemic variability. This method integrates both minor and major fluctuations but does not permit differentiation of the major from the minor ones.

The Mean Amplitude of Glycemic Excursions (MAGE) index is the most comprehensive index for assessing intraday glycemic variability; it is obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs, as long as the differences are greater than one SD of the mean glucose value. Its determination requires continuous glucose monitoring, which detects all isolated upward and downward acute glucose fluctuations. The advantages of MAGE are that it is independent of the mean glucose value and is designed to quantify major glucose fluctuations and exclude minor fluctuations [65].

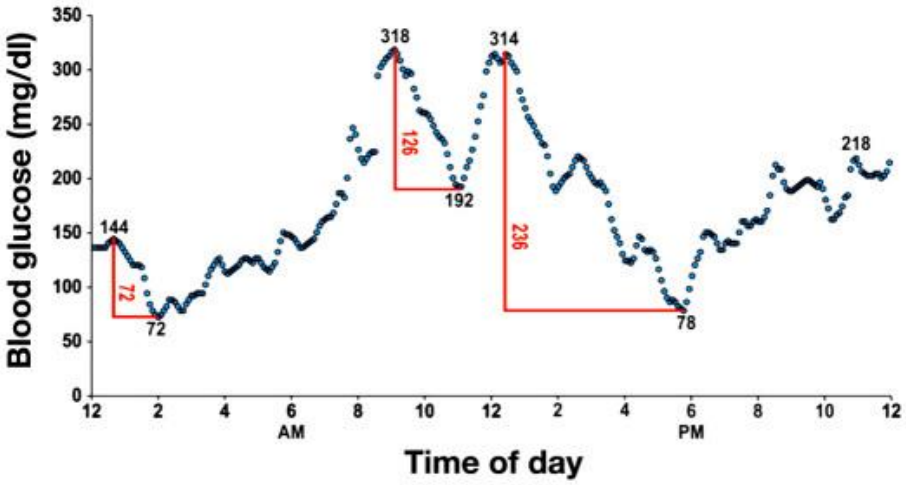

Figure3: Example of MAGE calculation; cited by Characterizing Blood Glucose Variability Using New Metrics with Continuous Glucose Monitoring Data

The mean absolute glucose (MAG) index takes into account all glycemic variations over time—even those remaining in the physiological range—and is obtained by calculating the absolute increments and decrements of glucose from peaks to nadirs per hour. This

measure includes minor as well as major glucose swings and time axis as the coordinate, it does not permit assessment of the real magnitude of glycemic excursions but rather their kinetics[66].

4. ACS AND HYPOGLYCEMIA

As explained before, if concerns regarding side effects on newborns after repeat course of steroids exist, a single course of ACS is considered to be safe. Nevertheless, the ALPS trial, first demonstrated that the risk of neonatal hypoglycemia is major in late preterm newborns exposed to ACS during fetal life compared with newborns not exposed [33].

Many subsequent studies have confirmed this finding not only among late preterm newborns but also at younger gestational age [67], [68]. Hypoglycemic events seem to develop especially during the first days after birth, probably because maternal corticosteroid-induced hyperglycemia leads to fetal hyperinsulinemia and subsequent neonatal hypoglycemia [67]. A German study evaluated the blood glucose levels in women exposed to ACS administration and found that glycemia was elevated for the first two days after prophylaxis administration, returning to the normoglycemic range on day 3 [69]. This finding suggests that a recent ACS administration is a risk factor for developing hyperglycemia in the mothers and subsequent hypoglycemia in the newborns.

However, the correlation between hypoglycemic events and the interval between the steroid dose and the time of delivery is not defined yet; also, the correlation between hypoglycemia and type of steroids administration (complete or incomplete) remains unclear.

PURPOSE OF THE STUDY

The main aim of this study is to evaluate glycemic control through continuous glycemic monitoring in preterm infants born from mothers who received the corticosteroids prophylaxis during pregnancy to induce lung maturation.

The second objective is to assess whether there are differences in glycemic trends according to the time elapsed between prophylaxis administration and the date of delivery.

The tertiary objective is to describe whether differences exist in glycemic control after corticosteroid exposure in utero, depending on gestational age.

Finally, this study describes the respiratory outcome and complications of infants exposed to prenatal prophylaxis compared with those of unexposed.

MATERIAL AND METHODS

1. Study design and patients:

This is a prospective single-center cohort study performed in the level-3 neonatal intensive care unit (NICU) of Giannina Gaslini Institute (Genoa).

Premature infants admitted in our unit with a gestational age between 31+0 and 34+6 weeks and a birth weight > 1000 g were enrolled in the study. Recruitment was among patients born at the Obstetrics Department of the Giannina Gaslini Institute or outborn patients admitted to our department for therapeutic management.

The exposition to antenatal steroid administration to induce lung maturation during the pregnancies was evaluated; variables among the exposition included the complete or incomplete steroid administration, and the distance between steroid administration and the date of birth.

In the Obstetric Departments of the Giannina Gaslini Institute and in the other Obstetric Departments that refer to our center, antenatal corticosteroids prophylaxis is performed to all women between 24 weeks and 34 weeks of gestation who are at risk of preterm delivery within 7 days, administering two doses of 12 mg intramuscular betamethasone every 24 hours.

The exclusion criteria from the study were: prenatal or neonatal diagnosis of any major congenital anomaly or metabolic/genetic/endocrine disorder, neonatal hypoxic ischemic encephalopathy, and maternal steroids treatment due to other medical indications.

The newborns enrolled were divided into three groups based on corticosteroid prophylaxis: complete course, partial course, and control groups. The complete course of ACS included

two doses of intramuscular betamethasone every 24 h administered to the mother at any time during pregnancy; the partial course included one 12 mg dose. The mothers of the neonates in the control group were not exposed to corticosteroids before delivery, because they did not have the indications for ACS medication or did not have enough time to receive prophylaxis during emergency delivery.

Infants belonging to the complete course group were divided according to the distance between steroid administration and delivery, to study if this period had any influence on the glycemic trend: the first group of patients had received prophylaxis within seven days of delivery and the second group of patients had received it for more than seven days.

The complete course group was also stratified based on gestational age: infants born at ≥ 34 of gestational weeks and infants < 34 weeks of gestation.

Demographic data such as gestational age at birth, birth weight, neonatal gender, number of fetuses, mode of delivery, pregnancy history and delivery history, were collected. In addition, respiratory outcomes and the development of other complications during the admission to our department were evaluated.

All the neonates included in the study were monitored with continuous glycemic monitoring (CGM) in the first 24 hours of life for at least 48 hours. The CGM device had been set with active alarms for hypoglycemia (< 45 mg/dL) and hyperglycemia (>180 mg/dL); in case of hypoglycemia or hyperglycemia, the glucose infusion rate was changed by the physicians.

Hypoglycemic and hyperglycemic events and glycemic variability (expressed as SD, MAGE and MAG) were compared between the groups.

All preterm infants enrolled in the study were treated according to the standard of care appropriate for gestational age and birth weight.

2. Continuous glycemic control

Real-time Medtronic MiniMed MMT-7820WE Guardian Connect (Northridge, CA 91325 USA) professional continuous glucose monitors with Enlite sensors (Medtronic of Canada Ltd, Brampton, Ontario) were used in the study.

Sensors were placed as soon as possible after study enrollment, preferably within 6 hours of birth. After accurate site disinfection, they were inserted into the lateral part of the thigh and secured with a clear adhesive dressing.

The sensor is minimally invasive, soft, flexible, and disposable. This device is about 1 mm-wide and 10 mm-long, and it is mounted through a hollow needle. Continuous measurements were recorded for at least the first 48 hours of life.

In order to minimize the potential procedural stress and pain associated with sensor insertion, 0.5 mL of glucose 10% was administered to the patient, if he/she was not sedated for any other reason.

The CGM was calibrated using capillary blood glucose values measured by FreeStyle Optium Neo H glucometer (Abbott Healthcare, Massachusetts, USA). Calibrations were performed at least three times per day as per the manufacturer's instructions.

Every 5 min, 24 h a day, the sensor detects interstitial fluid blood glucose and stores it in the device, providing 288 interstitial glucose values per day. After completing the registration with CGM, the neonatologist removed the sensor. Data were downloaded onto a Windows-based notebook computer running Medtronic Diabetes software.

In case of detachment or malfunction, the device was replaced no more than once.

Infants were carefully monitored for the occurrence of adverse events at sensor insertion sites (such as irritation, subcutaneous hemorrhage and signs of infection).

The sensors appeared to be safe and well tolerated in our babies without any complication. It did not interfere with nursing care. The system was removed if the patient needed to be transferred to another unit or hospital.

Figure 4: sensor placed into the lateral part of the thigh

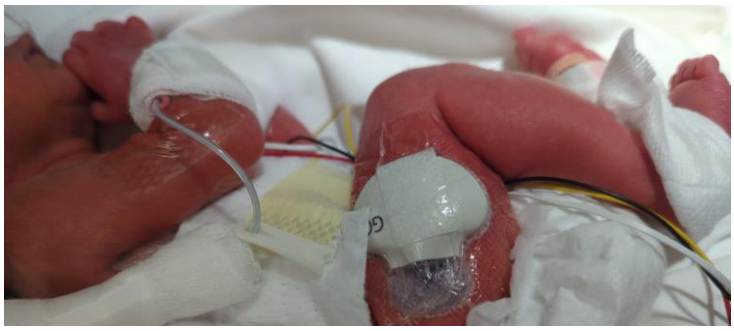

Figure 5: continuous glucose monitor

STATISTICAL ANALYSIS

Descriptive analysis was performed, and data were expressed as mean and standard deviation (SD), as median and range for continuous variables, and as absolute and relative frequencies for categorical variables.

Comparisons between groups were evaluated by nonparametric tests (Mann-Whitney U-test) for continuous variables. Association between categorical variables was performed using the $\chi 2$ test or Fisher's exact test. All p-values were calculated using two-tailed tests, considering a p-value less than 0.05 to be statistically significant. Statistical analysis was conducted using SPSS for Windows, version 20 (IBM SPSS Inc., New York, NY, USA).

Glycemic variability was measured by means of EasyGV software, available free for academic or noncommercial use at the www.phc.ox.ac.uk/research/technology-outputs/easygv website. EasyGV calculates several measures of glycemic variability from CGM data: we reported Standard Deviation (SD), Mean Amplitude of Glycemic Excursions (MAGE) and Mean Absolute Glucose (MAG).

During the monitoring, glycemic variability was calculated for each day recording.

RESULTS

Thirty-seven newborns met eligibility criteria for the study: twenty-six had received complete ACS course, six had been exposed to a partial course and five had not been exposed to prenatal prophylaxis.

Table 1 provides the characteristics of the newborns of the three groups. There were no statistically significant differences about sex, gestational age, birth weight, birth weight centile, IUGR, Apgar score, type of delivery and premature rupture of membranes. All infants born from twin pregnancies had received steroid prophylaxis and placental abruption is a more frequent condition in infants not exposed to ACS (p=0,01). It is more common that outborn patients have not been exposed to ACS or have received partial ACS (p= 0,02).

Table 1: baseline characteristics	**ACS Complete course N= 26**	**ACS Partial course N=6**	**ACS not administered N=5**	**P value**
Gestational age, weeks, Mean (SD)	32,98±1,12	32,65±1,60	33,94 ±0,93	0,19
Birth weight, Mean (SD)	1635,19±394,10	1893,3±577,65	1986,0±426,36	0,26
Centile, Mean (SD)	32,23±26,24	58,17±41,18	36,20 ±26,98	0,19
APGAR 1' **APGAR 5'**	6,88±2,21 8,27±1,48	5,67±2,16 7,67±1,03	6,40±2,07 8,00±1,41	0,23 0,20
Sex, M (%)	13 (50)	3 (50)	3 (60)	0,92
Delivery mode **Spontaneous vaginal delivery (%)** **Cesarean section (%)**	 3 (11,5) 23 (88,4)	 1 (16,7) 5 (83,3)	 1 (20) 4 (80)	 0,85
Twins, yes (%)	14 (23,8)	0	0	**0,009**
IUGR (%)	9 (34,6)	2 (33,3)	0	0,29
pPROM (%)	3 (11,5)	2 (33,3)	0	0,24
Placental abruption (%)	1 (3,9)	1 (16,7)	3 (60)	**0,01**
Outborn, yes (%)	3 (11,5)	3 (50)	3 (60)	**0,02**

Table 1. Clinical characteristics of the study patients
p Values were calculated to assess differences between newborns of the three groups

Regarding complications (table 2), there were not statistically significant differences in the groups in sepsis, IVH and NEC. As expected, infants not exposed to ACS presented a higher intubation rate (p=0,03).

Table 2: patients' complications and respiratory outcome	ACS complete course N=26	ACS partial course N=6	ACS not administered (control group) N=5	p value
Sepsis (%)	1 (3,8)	0	0	0,8
Intraventricular hemorrhage (%)	2 (7,7%)	0	0	0.64
Necrotizing enterocolitis (%)	0	0	0	/
Endotracheal intubation (%)	6 (23,1)	1 (16,7)	4 (80)	**0.03**
Day of life to reach spontaneous breathing (Mean ± SD)	8,77 ± 8,12	6 ± 3,22	7,8 ± 3,96	0,69

Table 2. Patients' complications and respiratory outcome
p Values were calculated to assess differences between newborns of the three groups

Six patients presented with episodes of hypoglycemia during the period of glycemic monitoring and five presented with episodes of hyperglycemia. The newborns who developed hypoglycemia had all received the complete ACS (23% of the ACS group).

As shown in Table 3 we observed that all the hypoglycemic events registered during the first day of monitoring occurred in infants who were exposed to complete ACS, so the difference between the groups is statistically significant (p= 0,0001); the hyperglycemic events are more frequent in infants not exposed to ACS (p=0,01). These events are less frequent during the second day of monitoring and the difference is no more statistically significant.

Table 3: hypoglycemic and hyperglycemic episodes	ACS complete course	ACS partial course	ACS not administered	p value
number of detection 1st day	6486	1532	1334	
< 45 mg/dl (%)	47 (0,7)	0	0	0,0001
< 47 mg/dl (%)	74 (0,8)	0	0	0,0001
> 180 mg/dl (%)	17 (0,3)	0	5 (0,4)	0,01
number of detection 2nd day	6499	1261	1468	
< 45 mg/dl (%)	7 (0,1)	0	0	0,12
< 47 mg/dl (%)	10 (0,2)	0	0	0,23
> 180 mg/dl (%)	0	0	0	/

Table 3: Number of hypoglycemic and hyperglycemic episodes in the three groups .

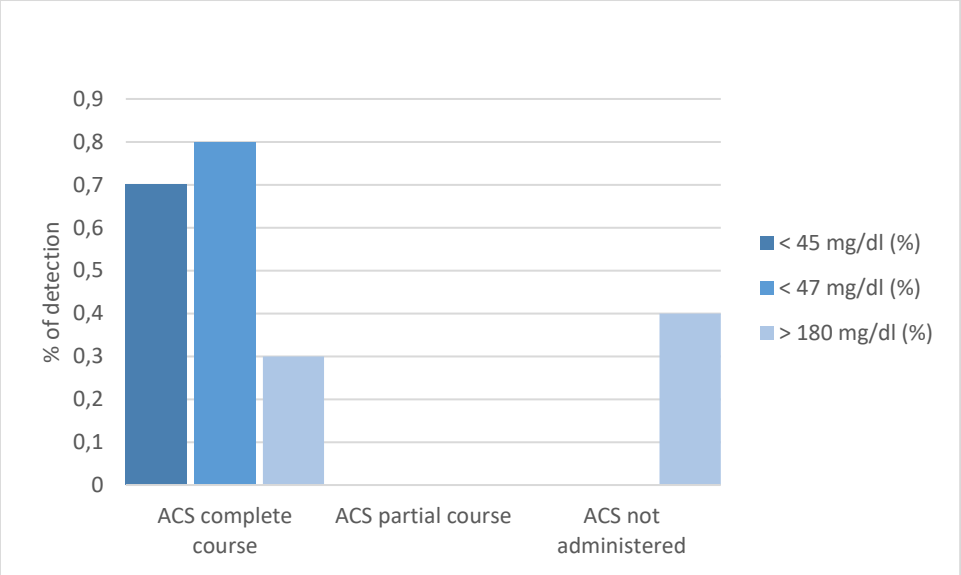

Figure 6: Hypoglycemic and hyperglycemic episodes in the three groups during the first day

To calculate the glycemic variability we used MAGE index, which is probably the most appropriate tool for selecting the major glucose swings that are calculated as the arithmetic mean of differences between consecutive peaks and nadirs. MAGE was calculated separately for each day of monitoring. The differences between the three groups are not statistically significant, but we observed a higher index of variability, with higher standard deviation, in the group of infants who were exposed to complete ACS.

Table 4: Index of glycemic variability	MAGE (±SD)			
	ACS complete course	ACS partial course	ACS not administered	p value
Day 1	11,71 ± 12,42	6,33 ± 5,85	7,2 ± 8,84	0,48
Day 2	9,85 ± 8,22	6 ± 6	9,73 ± 11,31	0,60

Table 4. MAGE index to calculate glycemic variability in the three groups.

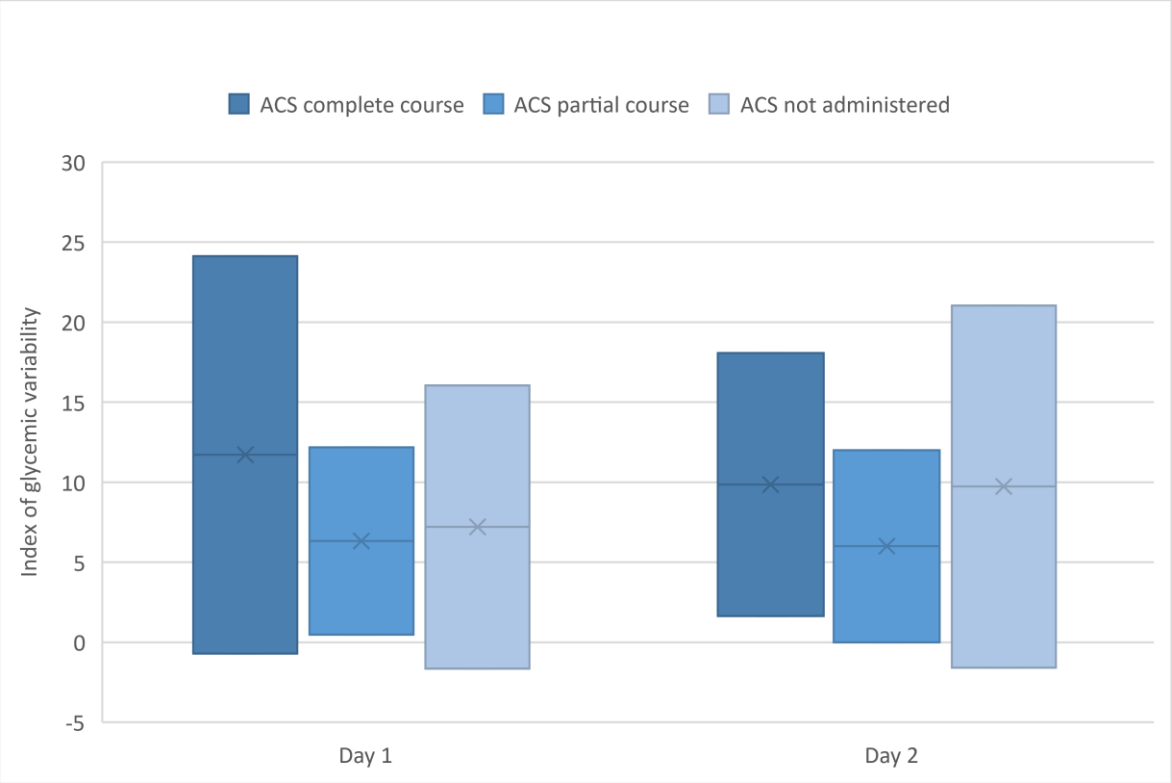

Figure 7: MAGE index to indicate glycemic variability in the three groups.

Considering the group that received the complete ACS (N=26), seventeen infants had been exposed within seven days from delivery and nine had been exposed to prophylaxis for more than seven days. We observed that all the hypoglycemic events registered occurred in the group of newborns exposed to ACS within seven days, so the difference between the two groups is statistically significant (p= 0,0001); instead, there is no significant difference in terms of hyperglycemic events. Also in this case, the difference is no more significant in the second day of life.

Table 5: hypoglycemic and hyperglycemic episodes and time of ACS administration	ACS ≤ 7 days N= 17	ACS > 7 days N= 9	p value
number of detection 1st day	4763	1723	
< 45 mg/dl (%)	47 (0,7)	0	0,0001
< 47 mg/dl (%)	74 (1,6)	0	0,0001
> 180 mg/dl (%)	11 (0,2)	6 (0,1)	0,41
number of detection 2nd day	5073	1426	
< 45 mg/dl (%)	7 (0,19)	0	0,36
< 47 mg/dl (%)	10 (0,2)	0	0,13
> 180 mg/dl (%)	0	0	

Table 5. hypoglycemic and hyperglycemic episodes in relation to the distance between complete ACS administration and delivery

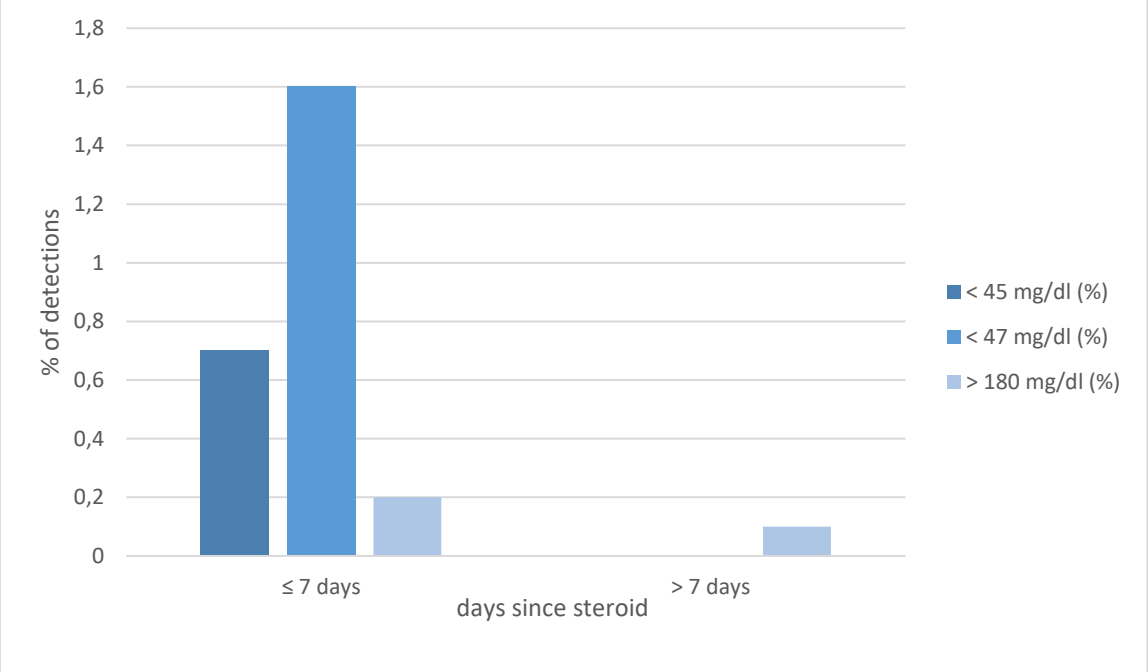

Figure 8: hypoglycemic and hyperglycemic episodes in relation to the distance between complete ACS administration and delivery during the first day

MAGE index (table 6) is not different in the two groups.

Table 6:	MAGE ± SD		
	ACS ≤ 7 days	ACS > 7 days	p value
Day 1	11,98 ± 13,24	11,19 ± 11,45	0,88
Day 2	8,38 ± 8,56	12,61 ± 7,19	0,22

Table 6. MAGE index in relation to the distance between complete ACS administration and delivery

Finally, dividing the group that received the complete ACS by gestational age, twenty patients were born before 34 weeks of gestation, six at 34 weeks or after. Studying this populations separately, we confirmed in both of them the data of higher number of hypoglycemic events (p= 0,0001 < 34 and p=0,005 ≥ 34) during the first day of monitoring in infants who were exposed to complete ACS compared with newborns partially exposed or not exposed.

Comparing the two populations, infants born before 34 weeks presented a statistically significant higher number of hypoglycemic (p = 0,05) and hyperglycemic events (p= 0,01) in the first day of monitoring (table 7).

Table 7: hypoglycemic and hyperglycemic events and gestational age	< 34 weeks of gestation N= 20	≥ 34 weeks of gestation N= 6	p value
number of detection 1st day	4041	2445	
< 45 mg/dl (%)	36 (0,9)	11 (0,4)	**0,05**
< 47 mg/dl (%)	56 (1,4)	18 (0,7)	**0,02**
> 180 mg/dl (%)	17 (0,4)	0	**0,01**
number of detection 2nd day	4302	2197	
< 45 mg/dl (%)	6 (0,1)	1 (0,0)	0,43
< 47 mg/dl (%)	9 (0,2)	1 (0,0)	0,18
> 180 mg/dl (%)	0	0	/

Table 7. hypoglycemic and hyperglycemic episodes in relation to gestational age at birth

Again, the glycemic variability does not show any statistically significant differences, but we can observe that during the first day of monitoring, the population of infants born < 34 weeks of gestation present a major glycemic variability expressed by a greater MAGE index with an important standard deviation.

Table 8:	MAGE ± SD		
	< 34 weeks of gestation	**≥ 34 weeks of gestation**	**p value**
Day 1	12,26 ± 13,99	9,87 ± 4,7	0,69
Day 2	8,84 ± 8,42	13,19 ± 7,19	0,26

Table 8. MAGE index in relation to the gestational age

DISCUSSION

The present study shows that the probability of hypoglycemic events in preterm newborns may increase after exposure, during fetal life, to a complete course of ACS administration to induce lung maturation. These events occur especially in the first 24 hours of life, and the effect of ACS on blood glucose levels seems to be related to prophylaxis administration within seven days from birth.

The ALPS trial (Antenatal Late Preterm Steroids), a double-blind placebo-controlled study, conducted in 17 MFMUs (Maternal-Fetal Medicine Units) of the United States found that the steroids administration determines a significant increase in neonatal hypoglycemia in late preterm infants [33]. After the ALPS trial other studies, including a meta-analysis, reported a significantly higher rate of hypoglycemia in late preterm newborns exposed to ACS [44], [45], [70]. Our study is in line with these previous findings, however, as shown in a recent multicentric cohort study by di Pasquo et al. [68], we found that the risk of hypoglycemia is higher after ACS exposure not only in late preterm babies but also at younger gestational ages. Regarding this result, it should be noted that low gestational age is a risk factor itself for the development of hypoglycemia, so it should be considered a confounding factor.

While the study by Di Pasquo affirmed that the type of ACS exposure (completed/partial) and interval between ACS administration and delivery do not affect the occurrence of neonatal hypoglycemia, conversely, we found a correlation between hypoglycemic events and complete ACS course and with steroids exposition within seven days from birth.

Instead, infants that had been exposed to corticosteroids more than seven days before delivery seem to present a more stable glycemic trend.

This finding is in line with what is known about the benefit of steroids on lung maturation that seem to decrease after 7 days from administration; the reduction of the steroidal effect would be evident not only on the minor benefits on respiratory function, but also on the minor rate of hypoglycemic events.

Regarding the period at greatest risk of developing hypoglycemia, a recent retrospective study describes a significantly lower blood glucose level in preterm babies who were exposed to ACS, during the first 12 hours of life[71]; our data suggest that the time in which hypoglycemia is more common is not only during the first 12 hours but is prolonged to the first 24.

The pathophysiological mechanisms of ACS-related neonatal hypoglycemia are not completed explained yet, but some studies suggested that there are two main mechanisms that could be potentially implicated [67], [71], [72]. First of all, the steroids administration may cause hyperglycemia in mothers who received the treatment, and this maternal hyperglycemia could lead to pancreatic beta cell hyperplasia and hyperinsulinemia in the fetus with subsequent hypoglycemia during the neonatal period [67]. Another possible cause is the suppression of the fetal pituitary adrenal axis that decreases the capacity of cortisol stress response [72].

As explained before, detection and management of hypoglycemia in newborns is crucial since, even if its long-term consequences are not yet well determined, they have been associated with increased risk of visual motor impairment and executive dysfunction in early childhood and with an increased risk of literacy and numeracy problems in later childhood [56].

Also, the identification of sustained hyperglycemia and glycemic variability is of our interest since it has been shown that they are connected with oxidative stress [63], that seems to have a major role in the pathogenesis of many neonatal diseases, including periventricular leukomalacia, bronchopulmonary dysplasia, and retinopathy of prematurity [64].

In our study we found that in the group exposed to complete ACS, hyperglycemic events are more frequent in newborns born before 34 weeks of gestation.

This finding could be explained by the fact that preterm babies present a small mass of insulin-dependent tissue (muscle and fat) with a consequent intracellular glucose deprivation, that may start counterregulatory responses and catabolism, leading to hyperglycemia [58]. It must be considered also the iatrogenic cause, the use of intravenous glucose infusions given at rates exceeding normal infant glucose turnover rates [57].

We used MAGE as index of glycemic variability as it is the most comprehensive index for assessing the intraday glycemic variability, because it is not dependent on the mean glucose value, and it is designed to quantitate major glucose swings and exclude minor one [65]. In our experience, we found an important numerical difference in MAGE index during the first day of life between the three groups of patients (ACS complete, incomplete, not administrated), although the difference is not statistically significant, probably due to the low sample size of the control groups.

Certainly, the small size of the populations, and in particular of the comparison groups, is a very important limitation of this study and of course a larger sample size is needed to confirm our finding about the correlation between hypoglycemic events and complete and recent ACS administration.

This limitation may be partly explained by the fact that in women at risk of delivery before 34 gestational weeks, ACS is routinely administrated. Consequently, the infants not exposed to ACS are only those born from preterm deliveries due to acute and unpredictable causes, such as placental abruption.

In a European cohort study of 4594 infants is found that only 14% of early preterm infants were not exposed to antenatal ACS; for this reason, existing literature on metabolic effects of ACS on preterm infants is mostly based on small retrospective experience [73].

Also in our study, the population of unexposed infants is small and consists mostly of outborn babies born from placental abruption, in whom therefore preterm birth was unexpected. None of the infants born from placenta abruption presented a clinical picture of perinatal asphyxia that could be a confounding factor in the development of hypoglycemic events.

Another limitation of the study is that glycemic monitoring was limited to the first 48 hours of life, and the possible long-term effect of ACS on glycemic control is not assessed.

Finally, in our experience, we focused on changes in blood glucose levels without studying the blood concentration of glucose- regulating hormones at the same time, which could be an interesting development to better understand the pathophysiology of glycemic instability after ACS administration.

The main strength of this work is the use of CGM to evaluate the glycemic trend and correlate it with ACS. In fact, most previous studies that focused on these correlations used intermittent blood glucose screening.

Continuous monitoring has been proven to be safe and to improve glycemic control in very preterm infants by increasing euglycemic time. Moreover, its use decreases the frequency of blood sampling and hence the number of heel pricks performed [74].

Therefore CGM utilization could be considered as an instrument to perform a strict glucose monitoring in the population at risk of developing hypoglycemic and hyperglycemic events, particularly in the first hours of life.

Finally, it is important to underline that hypoglycemia is a minor side effect compared with the beneficial effects of ACS administration on neonatal outcome, particularly in infants born before 34 gestational weeks. Therefore, what we found is useful in stressing the importance of proper glycemic monitoring after birth, especially at low gestational ages.

CONCLUSIONS

Antenatal corticosteroids administration to induce lung maturation may increase the rate of hypoglycemic events in preterm infants within 24 hours of birth; moreover, prophylaxis administered within seven days of birth seems to be correlated with the hypoglycemic condition. Therefore, strict glucose monitoring, especially on the first day of life, is recommended for all preterm infants (both < 34 and late preterm) with a history of recent ACS exposure. Continuous glycemic monitoring could be a useful instrument to check the glycemic trend and detect not only hypoglycemic and hyperglycemic events but also glycemic variability.

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