Difference in perinatal outcome of pregnancies with late preterm birth and early term birth

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DIPLOMA THESIS

Academic year:

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1. INTRODUCTION

1.1 Definitions and Terminology

The physiological duration of a human pregnancy is 40 weeks (280 days). This manner of counting starts on the first day of the last menstrual period of the mother. Forty weeks after that day the delivery of the child is understood as physiological and the child is described as being born 'full-term' or 'at term' (1).

According to the WHO, The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists preterm birth is defined as the delivery of an infant before 37 completed weeks or 259 days of gestation, while birth between 37 and 42 completed weeks of pregnancy is considered to be term birth (2,3). In the past decades it was assumed, that within the period of term births outcomes were homogenous and favorable (4). During recent years research has increasingly shown that perinatal outcomes differ even within the time span of the 5 weeks considered to be term birth and also, as one would suspect, among preterm infants depending on the time of delivery (5). With the definitions of preterm and term mentioned before no distinction is being made among different intervals within the two groups of preterm and term birth, so to address and be able to more accurately describe these observations more specific subcategories were instituted and the terms Late Preterm and Early Term were established. During a workshop of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development in 2005 the panel of the invited group of experts decided that the previously used expression “near term” should be abandoned and the term “Late Preterm” was coined for infants born between 34 weeks of gestation and 36 $^{+6/7}$ weeks of gestation. (6). More recently, in 2013, The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine discouraged the use of the general label „term pregnancy“ and suggested replacing it with more specific labels, dividing the 5-week time span of the so-called term period into 4 categories: „early term“ (37 weeks – 38 $^{+6/7}$ weeks), „full term“ (39 weeks – 40 $^{+6/7}$ weeks), „late term“ (41 weeks – 41 $^{+6/7}$ weeks), and „postterm“ (42 weeks and beyond) (4) .

The aims of defining late preterm and early term were to create the possibility to more accurately describe the perinatal and long-term outcomes, develop optimal care strategies, define causes for deliveries at these gestational ages and improve the quality and specificity of data collection in order to encourage and improve clinical research (4,5).

1.2 Epidemiology

Preterm birth is a global problem. The 10 countries with the highest numbers of preterm deliveries include Brazil, the United States, India, and Nigeria. Still, low-income countries have higher percentages of preterm births than developed countries, and within countries families with lower socio-economic status are at increased risk of having a preterm child (7). Also, the rates of preterm birth in developed countries have been rising constantly in the past years (8). As stated by the WHO, approximately 15 million infants are born preterm every year, with rates ranging from 5 – 18 % in different countries worldwide. Specifically, Davidoff et al. l found that 66% of the increase of preterm births from 1992 to 2002 in the United States were due to an increase in LPT births (9). In 2008, 12.3 % of all live births in the United States were classified as preterm births and of these preterm infants approximately 75 % were born late preterm (8,10). In total there has been an increase from 7,3% to 9,14 % of all live births being born as late preterm, which marks an increase by 25 % in the past two decades (5).

Correspondingly, early term births make up 17,5 % of all live births in the US with a reported increase of 21% from 1990 to 2008 (8,11).

Despite the global trends of increasing numbers of preterm births, according to the Global Action Report on Preterm Birth by the WHO in 2012, Croatia is one of three countries that have had an estimated reduction in preterm birth rates in the period from 1990 – 2010. The report states that Croatia is one of the few countries that even shows a decline in preterm deaths within one decade. According to UNICEF, approximately 2300 children are born preterm in Croatia annually, with 300 to 400 of them requiring intensive medical treatment. This constitutes a preterm birth rate of 5,5 % in Croatia (7).

Several studies have found that Late Preterm infants have higher rates of neonatal morbidity and mortality, more frequent NICU admissions and an increased risk of long-term health problems which need medical attention and other support systems when compared to term children (7,8,12). So, with them making up a large percentage of the preterm birth group, even a small increase in the numbers of LPT births will have a big influence on health care costs. This is also the case in ET births. These infants have increased risk for respiratory disorders and neonatal mortality in comparison to children born an later gestational ages, which are associated with higher rates of admission to the intensive care unit after birth (8,13).

Admissions to the neonatal intensive care unit comprise a considerable economic burden, costing the health care system up to 3500 $ per day (14). One study done in California showed that the state could save almost 50 million $ in one year if the number of non-medically indicated deliveries in the late preterm and early term period were lowered (15).

Aside from the economic concern, it is important not to underestimate the social and emotional hardship that families of LPT and ET babies have to pay when facing the possible complications associated with birth at these gestational ages and enduring emotionally and physically stressful hospital stays of their child or even experiencing the sudden loss of their newborn child (7).

Reasons for the rises in the rates of late preterm and early term deliveries are believed to be the increasing numbers of medically indicated deliveries, the growing percentages of multiple pregnancies due to IVF, and the increase in late primiparity in recent years (13).

1.3 Health Risks for the Neonate

According to the WHO prematurity is the second leading cause of child mortality under the age of five worldwide and the most important cause of death in the first month of life (7).

Most studies about the neonatal outcome of prematurely born children conducted in the past have looked at preterm infants in general, especially those born before 33 weeks of gestation (8,13). Recently there have been several studies suggesting that late preterm infants as well as early term infants also are at increased risk of short-term and long-term consequences of being born at these earlier gestational stages (11,13). Late preterm neonates have been shown to have 3.5 times more clinical problems than term neonates and a 4.6 times higher mortality rate, while early term babies as well seem to have an increased risk of morbidity, specifically respiratory problems, when compared to babies born after 38 completed weeks of pregnancy (5,8).

Generally, late preterm infants have higher numbers of admission to the neonatal intensive care unit, hospital readmissions and longer hospital stays than babies born at full term. More specifically, they are at increased risk for respiratory morbidities, temperature instabilities, hypoglycemia, sepsis, hyperbilirubinemia, necrotizing enterocolitis, neurological morbidities, and mortality (16). Because of their immaturity late preterm infants often fail to

adequately adapt to extrauterine life within the first 12 hours of life, which leads to increased rates of hypoglycemia and hypothermia in these children (17). The brain of fetuses undergoes dramatic maturation in the last 4 weeks of pregnancy, which is why late preterm children often have significantly immature brains compared to neonates born at term (18). Due to higher risk for prolonged physiological jaundice of the newborn in late preterm children, they are also more susceptible to hyperbilirubenemia-induced brain damage or kernicterus (6).

Long-term outcomes that have been observed in children born at the late preterm stage are a generally increased infant and young adult mortality, higher rates of cerebral palsy and mental retardation, childhood asthma, learning difficulties, schizophrenia, and diabetes mellitus in young adults (13).

Early term infants similarly have been shown to have an increased risk of admission to the intensive care unit, hospital readmission, and longer stays in the hospital after birth (16). Cheng et al. observed that infants born at 37 and 38 weeks of gestation have a significantly higher risk of hyaline membrane disease (or respiratory distress syndrome of the newborn) than those born at 39 to 41 weeks of gestation (19).

In general it has been found, that there is an inverse relationship between the risk of respiratory distress and gestational age as well as between the length of the hospital stay of infants after birth and gestational age (5,20).

The largest group of morbidities in late preterm infants as well as in early term infants are respiratory morbidities. Mohan et al. showed that late preterm infants have a 9-fold and early term infants a 5-fold increased risk to develop respiratory distress after birth when compared with infants born after 38 weeks of gestation (14).

1.4 Physiology of lung maturation and problems with preterm birth

The maturity status of the fetal lung is very important in regard to the probability of respiratory complications of the fetus after birth. This refers to the anatomical and morphological maturity of the fetal lung as well as the functional maturity. Anatomical maturity is reached at approximately 32 weeks of gestation when the final 'alveolar stage' of lung development begins. In this stage the epithelial lining of the alveoli starts to become thinner, an extracellular matrix, a capillary network and the lymph system develop, and the type II pneumocytes start producing surfactant (1). Functional maturity of the fetal lung on

one hand depends on the ability of the lung to produce surfactant and on the other hand on fluid secretory pathways across the lung's apical membranes (1).

Surfactant is produced by type II pneumocytes in the lungs and its function is to keep the terminal sacs from collapsing by reducing the surface tension of the alveoli after birth (1). The primary components that contribute to the surface tension-lowering properties of surfactant are glycerophospholipids, which make up around 90 percent of the surfactant's dry weight. Apoproteins promote the forming and re-forming of a lining with surfactant in the alveoli during respiration. The major known apoprotein in surfactant is Surfactant Apoprotein A (SP-A). In maturing fetal lungs there is increased secretion of SP-A which leads to increased surfactant production. Simultaneously there is also an increased SP-A concentration the amniotic fluid. This SP-A concentration in the amniotic fluid is being used as an indicator of fetal lung maturity when amniotic fluid is examined using amniocentesis (1).

Another important physiological mechanism in the maturing fetal lung is the secretion of fluid into the alveoli. During gestation there is active secretion of fluid into alveolar spaces in the lungs of the fetus. This secretion is facilitated via a chloride secretory mechanism and is important for the fetal lung development (21). As the pregnancy approaches term there is a decrease in fluid production and a change in direction of flow of fluid. This causes fluid to be transferred from the lumen into the interstitial space across the apical membrane and the fluid is absorbed into the pulmonary circulation (22). This change in the course of physiology is due to an increased expression of epithelial sodium channels (ENaC) and passive movement of sodium through those ion channels (23). In addition, there is a decreased flow of liquid into the lumen due to decreased chloride secretion across the epithelium (24). The transformations in the physiology of the fetus are brought about by changes in the hormonal milieu of the fetus and the mother, mainly by a surge of endogenous steroids and catecholamines around the term of the pregnancy as well as during vaginal delivery (25).

Taking these physiological events from the perinatal period into account it becomes clear that one way to prevent respiratory difficulties after birth in fetuses at risk to be born preterm, is to facilitate the sodium reabsorption of their lung epithelium and thus drive water out of their alveoli and to promote surfactant production (22). In 1972 Liggins and Howie first found that this can be done by replacing the endogenous surge of steroids, which has not taken place in imminent preterm labor, by exogenous glucocorticoids (26). These will, administered to the mother intramuscularly, increase the expression of endothelial sodium

channels in the lungs of the fetus which will promote the passive movement of sodium as well as augment the surfactant production (1,23).

Up until recently most studies focused on the administration of antenatal steroids to mothers before 34 weeks of gestation and found favorable outcomes in regard to lung maturity of preterm children. The systematic review done by Roberts et al. showed that antenatal steroids decrease most serious adverse outcomes due to prematurity, like perinatal death, neonatal death, intraventricular hemorrhage, necrotizing enterocolitis, need for mechanical ventilation, systemic infections in the first 48 hours of life and respiratory distress syndrome (27). These results can be attributed to the actions of the glucocorticoids which have several effects, including those on the lung physiology of the fetus: The production of surfactant is increased, and the removal of fluid from the lung by the before mentioned mechanisms is facilitated (21).

At the NIH conference in 1994, and additionally in many practice recommendations of the obstetric societies, the consensus was established that antenatal steroids should be administered to women at risk to deliver before 32 – 34 weeks of pregnancy (28). More recently several studies suggested to apply antenatal steroids to mothers at risk of late preterm delivery as well, since it has been shown that these children have increased rates of respiratory distress due to transient tachypnea of the newborn and surfactant deficiency for example (25,29). In August 2017 the Committee for Obstetric Practice by the American College of Obstetricians and Gynecologists published a committee opinion with the recommendation to administer a single course of betamethasone to pregnant women between 34 0/7 and 36 6/7 weeks of gestation who are at risk to deliver within the next 7 days (30). This recommendation is principally based on the results of the 'Maternal Fetal Medicine Units Network Antenatal Late Preterm Steroids Trial', which showed that late preterm infants exposed to betamethasone had significantly lower rates of transient tachypnea of the newborn, bronchopulmonary dysplasia, and respiratory distress syndrome as well as a lower risk of requiring respiratory support or immediate postnatal resuscitation (31).

1.5 Reasons for LPT and ET deliveries

According to Williams et al., four main direct reasons are responsible for preterm birth: Spontaneous preterm labor with intact membranes, idiopathic preterm premature rupture of membranes, delivery for maternal or fetal indications, and multifetal pregnancies,

with 30 - 40% of all preterm births being medically indicated and 40 – 45% being spontaneous (1). During the workshop of the NICH, the committee ascertained that in most academic centers the majority of late-preterm births are medically indicated (6).

Maternal conditions that entail an indicated termination of the pregnancy before 38 completed weeks of gestation are for example preeclampsia and placental abruption. Conditions in which there is impending or actual fetal compromise, like oligohydramnios or intrauterine growth restriction (IUGR), are also indications for iatrogenic preterm pregnancy termination (5).

Brown et al. determined and classified the risk factors for spontaneous late preterm delivery into four categories: Infection and Inflammation, Placental ischemia and other hypoxia, Endocrine triggers, and "Other" (16). This is in concordance with the theory that chorioamnionitis, hypertension and preterm premature rupture of membranes (PPROM) are risk factors for late preterm birth and early term birth (5). It has also been shown that pregestational diabetes is more common in mothers giving birth in late preterm and early term stages of gestation than in those giving birth after 38 completed weeks of gestation (5).

The negative perinatal outcomes of late preterm and early term infants described earlier can comprehensibly be attributed to the physiological and metabolic immaturity of the infants. Several authors have suggested that the maternal complications, that are often the underlying reason for preterm delivery at those gestational ages, also contribute to the adverse perinatal outcome of late preterm and early term infants in an extend which is yet to be determined (8,16).

1.6 Parameters to Assess Perinatal Outcome

1.6.1 Age of the mother

Both, pregnancies in women older than 35 years as well as pregnancies in adolescent women have been increasing in numbers in the past century (32). Gravena and colleagues showed that children born to adolescent (< 15 years old) women or women with late gestation (> 35 years old) are at increased risk of being born prematurely, having a low birth weight and Apgar scores below 7 (32).

1.6.2 Parity

Several studies suggest that adverse neonatal outcomes are more common in nulliparous women, especially when combined with advanced age of the mother (> 40 years). Baser et al.

found in their study that infants born to older nulliparous women have a higher risk of low birth weight, low Apgar scores, and admissions to the intensive care unit (33).

1.6.3 Delivery mode

For each delivery, doctors and the patient need to consider the risks and benefits of a spontaneous vaginal delivery or a cesarean section when making the decision about the route of delivery. Generally, vaginal delivery should always be anticipated, because it has been shown that the process of vaginal delivery has several important beneficial consequences regarding the health of the newborn. Exposure to the mothers vaginal and intestinal flora positively influences the immune system of the neonate by inducing its colonization and promoting production of cytokines (34). As mentioned previously the change in the hormonal milieu that accompanies the onset of spontaneous labor plays an important role in the final maturation process of the fetal lung, in the preparation of the fetus for the transition to extrauterine life and in clearing the lung from fluid. Clearance of fluid from the lung is also facilitated by mechanical factors and Sterling forces exhibited during vaginal delivery (25).

The rate of cesarean sections has been rising during the last decades globally as well as in Croatia. In Croatia, during the decade from 2000 to 2009 it increased by more than 60% to a rate of 17, 7% (35). In 2014 even 19, 9% of all deliveries were cesarean sections in Croatia (36).

Cesarean delivery may be indicated in several circumstances, like abnormal presentation of the fetus, multifetal pregnancy, or repeat cesarean section or it may become necessary during delivery due to non-reassuring fetal heart beats or cephalopelvic disproportion for example (11). Sometimes it is done solely due to the request of the mother without any medical indication. Previous studies have shown that cesarean delivery is associated with higher rates of neonatal mortality, longer stays at intensive care units, higher probability of respiratory problems and breast feeding difficulties (11,34).

1.6.4 Length and weight of the neonate; SGA, AGA, or LGA

The crown - heel length and the weight of the newborn should be measured within the first hour after delivery. These two measures are the most important anthropometric measurements in neonates in the peri- and postnatal period regarding the newborn's health and development (37). For term-infants normal crown-heel length is set at 48 – 54 cm with an average value of

50 cm, while the normal birth weight is considered to be between 2800 and 4100 g with an average of 3400 g (38). To be able to appropriately compare birth length and weight values they need to be adjusted to the gestational age. Corresponding curves give information about the respective percentiles regarding each gestational week and allow for determination of infants who are small for gestational age (SGA), appropriate (AGA), or large for gestational age (LGA) as classified by Lubchenko in 1967 (1). Infants placing below the 10th percentile are considered to be small for gestational age, while infants that lie above the 90th percentile count as large for gestational age infants. Children lying between the 10th and the 90th percentile are referred to as appropriate for gestational age infants (37). It has been shown that both small for gestational age infants as well as large for gestational age infants are at increased risk of having complications at birth, but also of developing cardiovascular diseases later in life as well as having metabolic difficulties (37).

The growth of the fetus is determined by several factors, like provision of nutrients by the mother, the adequate transfer of these substances via the placenta and by genetic predisposition. Thus it is important to comprehend that not all children lying below the 10th percentile do so for pathological reasons of growth restriction, but merely because of their intrinsic biological aspects (1).

1.6.5 Apgar Score

The Apgar Scoring System was invented in 1953 by Dr. Virginia Apgar as a tool to quickly assess the cardiopulmonary and neurological status of the newborn and to identify newborns that need resuscitation. It consists of five variables: Heart rate, respiratory effort, muscle tone, reflex irritability and skin color of which each is given a value of 0, 1 or 2 points. The sum of the five components makes up the total score, with 10 being the best possible and 0 describing a lifeless infant. The Apgar Score is determined at 1 minute after birth and again after 5 minutes. The 1- minute Apgar score indicates the necessity of resuscitation, while the 5-minute Apgar Score, and especially the difference between the two scores, is a good indicator of the effectiveness of the resuscitative efforts and the development of the wellbeing of the neonate (1). Casey et al. found that in term as well as in preterm infants 5-minute Apgar Scores of 3 or less predicted a neonatal death rate of 1 in 4, which allows the conclusion that the 5-minute Apgar Score is of prognostic value for neonatal survival (1).

When using the Apgar Score for evaluating preterm infants it is important to be aware of the fact that certain elements of the Apgar Score are closely related to the physiological maturity

of the newborn and thus a preterm infant, although healthy, may receive a lower Apgar score simply due to immaturity.

1.6.6 Umbilical Artery pH

As first described by James et al. in 1958, umbilical blood gas analysis can implicate fetal perinatal hypoxia and thus indicate the condition of the newborn and its outcome (39). Because of anaerobic glycolysis during prolonged hypoxia of the fetus, metabolic acidosis occurs in cases of intrapartal asphyxia (40). Thus, the blood gas analysis of umbilical arterial blood provides an objective measurement of the metabolic status of the newborn. Today it is recommended by the American College of Obstetrics and Gynecology that blood gas analysis of the umbilical blood should be performed in all high-risk deliveries (41). In some centers, like at our institution, the University Hospital of Split, the umbilical artery pH is obtained routinely after delivery. The pH of neonatal blood is determined by sampling blood from the umbilical artery from the umbilical cord from a segment which is clamped at two places right after delivery, so that the segment between the clamps is isolated from both the placenta and the environment. In this situation the pH of the umbilical blood will remain unchanged for approximately one hour. Normal pH values in healthy term newborns are in the range from 7,26 – 7,3 with comparable values having been found for preterm newborns. One of the main causes of fetal acidemia is decreased uteroplacental oxygenation. During labor, fetal oxygenation and pH generally decline as part of the normal course of labor and most children will tolerate pH values as low as 7,0 without suffering neurological damage. Values below 7,0 are associated with neonatal death, intensive care unit admissions, intubations, seizures, and neonatal encephalopathy (1).

2. OBJECTIVES

The aim of our study was to analyze if there is a difference in perinatal outcome between pregnancies with Late Preterm Birth and those with Early Term Birth.

We hypothesized that there is a significant difference in perinatal outcome between late preterm infants and early term infants in regard to the before mentioned parameters. We expected late preterm infants to have a worse perinatal outcome owing to their lower gestational week at birth and their decreased physiological maturity. Early term infants were expected to have a significantly better perinatal outcome since this group is considered to be term, hence mature, neonates.

3. METHODS

This retrospective cohort study was conducted in the Department of Obstetrics and Gynecology of the University Hospital of Split (KBC Split) of the University of Split, School of Medicine. Medical data of consecutive Late Preterm and Early Term births that took place from January 2016 to April 2016 were studied. Patient's medical records and data are stored in the record books of the delivery room and data for this study were collected from there. Infants born alive at gestational ages from 34 $^{+0/7}$ through 38 $^{+6/7}$ weeks were included in the study and following data were extracted from the data base:

1. Age of mother in years;
2. Parity of mother;
3. Pregnancy duration in completed weeks;
4. Weight of neonate in grams;
5. Length of neonate in cm;
6. Apgar Score (0-3; 4-7; 8-10);
7. Delivery mode (Vaginal or Cesarean Section);
8. Size of the neonate in relation to gestational age (SGA, AGA, LGA).

Size for gestational age was calculated using population adjusted percentile diagrams.

Chosen exclusion criteria were infants born with congenital anomalies, stillbirths, multiple pregnancies and pregnancies with unknown gestational ages.

For the statistical analysis of the data the statistical software STATISTICA 12 (StatSoft, Hamburg, Germany) was used. The normal distribution of data was tested with Kolmogorov-Smirnov Test. For comparison of data of the two studied groups Student's t-Test was applied for numeric and normal distributed variables, and Mann-Whitney U test for numeric variables without normal distribution. For non-numeric variables Pearson Chi square test was used and alternatively Fisher exact test. The significance level was set at $P < 0.05$.

4. RESULTS

Medical records of a total of 403 births were studied, of which 64 (15. 88%) were in the Late Preterm study group, and 339 (84. 12 %) were in the control group of Early Term births.

After the statistical analysis of the collected data we found that regarding age and pH there was no statistically significant difference between the two groups (p = 0.987 and p = 0.377 respectively). In the Late Preterm group, the mean age was 30.42 years (SD 5. 74), and in the Early Term group it was 30.43 years (SD 5. 30). So, the difference of the mean age between the investigated groups was 0.01 years, which does not represent a statistically relevant difference. The median pH in the Late Preterm group was 7,32 just like the mean pH in the Early Term group was 7,32. We did not find a statistically significant difference in umbilical artery pH values between the two investigated groups.

In parity, weight, and length we did find results with a statistical significant difference between the groups. The median parity in the Late preterm group was 1, while in the Early Term group it was 2 (p = <0.020). The mean weight in the Late Preterm group was 2696.72 g +/- 453.74 g, and in the Early Term group it was 3344.72 g +/- 473.31 g (p <0.001). The median length in the Late preterm group was 47 cm with an interquartile range of 46.00 – 48.00, in the Early Term group it was 50 cm with an interquartile range of 49.00 – 51.00 (p <0.001).

Regarding the delivery mode, we did not observe any statistically significant difference between the two studied groups (p = 0.170). The rate of vaginal delivery in the Late preterm group was 62,50 % compared to 71,09 % in the Early Term group. The cesarean section rate in the Late Preterm group was 37,50 % and in the Early Term group it was 28,91%.

We did find a statistically significant difference regarding the Apgar scores (p < 0.001) between the two groups. In the Late Preterm group 81,25 % had an Apgar score of 8-10, while in the Early Term group 97,64 % had an Apgar score in that range. 18,75 % of Late Preterm births had an Apgar score of 4-7, and only 2,36 % of Early Term groups had an Apgar score of that range.

Regarding the size for gestational age, in both studied groups the majority of infants were appropriate for gestational age (AGA). We found that in the Late Preterm group 88,71% were AGA, while in the Early Term group 84,13 % were AGA. 4.84% of Late Preterm infants were large for gestational age (LGA), and 9.88% of Early Term infants were large for

gestational age. In the small for gestational age category we found 6.45% of the Late Preterm infants and 5.99% of the Early Term infants. After using Chi-square test we found that there is no statistically relevant difference in these values ($p = 0.447$).

Table 1 Results of both study groups

	Late Preterm	**Early Term**	**P**
Age of Mother (Years)	30.42 ± 5.74	30.43 ± 5.30	0.987*
Parity	1.00†	2.00†	0.020‡
Fetal weight (grams)	2696.72 ± 453.74	3344.72 ± 473.31	< 0.001*
Fetal length (cm)	47†	50†	< 0.001‡
pH	7.31†	7.32 ± 0.08	0.377‡
Apgar score			< 0.001§
0-3	-	-	
4-7	12 (18.75 %)	8 (81.25 %)	
8-10	52 (2.36 %)	331 (97.64 %)	
Delivery mode			0.170§
Vaginal	40 (62.50 %)	241 (71.09 %)	
CS	24 (37.50 %)	98 (28.91 %)	
Size for gestational age			0.447§
SGA	4 (6.45 %)	20 (5.99 %)	
AGA	55 (88.71 %)	281 (84.13 %)	
LGA	3 (4.84 %)	33 (9.88 %)	

SGA = Small for gestational age
AGA = Appropriate for gestational age
LGA = Large for gestational age
* t Test
† Median
‡ Mann-Whitney Test
§ Chi square Test

5. DISCUSSION

After analyzing our data, we found that there is a difference in the perinatal outcome between children born Late Preterm and those born Early Term. This statement can be based on our finding that Early Term infants have better Apgar scores than Late Preterm infants.

The advantages of our study are the relatively big pool of data available since the Department of Gynecology and Obstetrics of KBC Split conducts births for a very large catchment area including some parts of Bosnia yielding 4266 births in the year 2016.

Our study had some limitations, especially regarding the continuity of complete data. Since the medical documentation is done manually and in an analogue way, not all data regarding all births are complete and for most births the medical information is not extensive. There was little to no information about maternal diseases before or during the pregnancy in the birth records at the delivery room as well as no information about any procedures that might have been done with the infant after birth.

The fact that in our study Early Term infants were significantly heavier and had a significantly longer body length than Late Preterm Infants is not surprising since these children had more time to grow in utero than the infants born at earlier gestational ages. Still, the birth weight has been shown to play a role in neonatal outcome. McIntire and colleagues found that, especially in term infants, morbidity and mortality were significantly higher if the child was below the 3rd percentile of weight for gestational age. Similarly, in preterm infants they observed a continuously increased risk of adverse perinatal outcomes with lower birth weight percentiles (42). Tamim et al. found in their prospective study that birth weights above 2750 g are associated with significantly lower rates of admission to the NICU (43). Taking into account this data we can say that there is a clinically relevant difference between our two studied groups regarding the birth weight with the Late Preterm group being at higher risk for morbidity and mortality due to the lower mean birthweight.

The mean maternal age was 30.42 and 30.43 years in the Late Preterm and Early Term groups respectively. Several studies have shown that advanced maternal age is a risk factor for adverse maternal and neonatal outcomes, but these findings usually refer to mothers being 35 years or older and adolescent mothers. The majority of mothers in our study did not belong to either of these groups and thus are not considered at higher risk for adverse outcomes due to their age (32,44,45).

In the Late Preterm group, the median parity was 1, in the Early Term group it was 2. While there are several studies suggesting that nulliparity is associated with a higher risk of

neonatal complications and prematurity this was almost exclusively found in mothers with advanced maternal age, meaning 35 years or older (33,44). Since the mean age of mothers in our study was below that value in both groups (see above) we can consider this a a low-risk factor in both groups.

The pH value in both our studied groups was 7.32. Umbilical cord pH is commonly used as an outcome measure both in clinical trials and by obstetricians to evaluate their work in the delivery room (46). Malin et al. showed in their systematic review and meta-analysis that low arterial umbilical cord pH has a strong association with neonatal morbidity and mortality (47). Specifically, studies have set the threshold value at a pH of 7.10, below which the risk for adverse neonatal outcomes, especially neurological ones, rises (48). The 'optimal' pH was set at 7.26 – 7.30 in this particular study, which is consistent with the generally accepted values used in delivery departments today (1). These values specifically apply to term newborns. Thus, the role of umbilical artery pH for predicting neonatal outcome in preterm infants might be less clear. In their cohort study Victory et al. established a relationship between increasing metabolic acidosis and adverse neonatal outcomes in preterm infants (49) and as stated previouly similar umbilical pH values are considered as 'cut-off' values for preterm infants like for term infants (1). Although it is debated if measurement of umbilical artery pH is the optimal measure of the neonate’s perinatal condition, it is currently a widely accepted technique of evaluating infants at risk or even routinely done in the perinatal setting and considered an important adjunct to assessment of the immediate and long-term perinatal outcome (40,47,50). From these points of view our results of no significant difference in frequency of acidosis between Late Preterm infants and Early Term infants, which are comparable to the results of Ramin et al., who studied the umbilical pH values of preterm and term infants, suggest that Late Preterm neonates do not generally have a higher risk of suffering from acidemia and consequently for having adverse neurological outcomes (51).

Prior et al. demonstrated the importance of the mode of delivery as a potential confounding factor in the assessment of perinatal outcome in conjunction with the other parameters of Apgar score and umbilical pH (52). We did not find any significant difference in terms of delivery mode in our two study groups. In both groups more children were delivered vaginally than by cesarean section and we did not find a correlation of the delivery mode with the gestational age. There is conflicting data about whether cesarean section in preterm infants is associated with a decreased or increased risk of neonatal morbidity (53,54).

In general, studies have shown that for uncomplicated pregnancies and deliveries vaginal delivery poses significant benefits and should be the preferred route of delivery (34). As stated previously, the cesarean section rate in Croatia is approximately 20 percent. In both groups in our study the rate of cesarean sections was higher than that (37.50% in the Late Preterm, and 28.91% in the Early Term group). These higher percentages could be explained by a higher incidence of medically indicated deliveries at these gestational ages which often lead to the decision of delivering the child by cesarean section. The underlying conditions leading to these medically indicated deliveries and their potential effect on the infant have to be considered when evaluating the outcome of these children. Unfortunately, this data was not available during our research, but we can say that the mode of delivery in our study does not contribute to a difference in the perinatal outcome between our two groups.

This is not the case with the Apgar scores. We found that there is a correlation between gestational age and Apgar score, with a significantly higher number of Early Term infants having a favorable Apgar score of 8-10 than Late Preterm infants, and significantly more Late Preterm infants having Apgar scores of 4-7. These findings are comparable to the results from Balayla et al., who also observed that Late Preterm birth is associated with greater odds of lower Apgar scores when compared to Early Term births, especially in the 35^{th} and 36^{th} week of gestation and to the results of Machado Jr. et al., who also found that Apgar scores in Late Preterm infants are significantly lower than those in term infants (13,55). This is in consistency with the conclusion Dolgun et al. made in their research, that Apgar scores increase with progressive gestational weeks (56). They also found that better Apgar scores were documented in preterm children born by cesarean section, which prompts the question if cesarean section should be the preferred mode of delivery for preterm births. However, Werner et al. published data that does not support the findings of Dolgun et al., saying that infants born by cesarean section had a higher risk of Apgar scores below 7 (53). When evaluating the Apgar score, it is important to bear in mind that Apgar scores are influenced not only by neonatal asphyxia but also by intrapartum use of analgesics (52). According to our findings and those of previous studies another factor affecting the Apgar score is prematurity (13,52,55). Despite the multifactorial influence on the value of the Apgar score, according to Heller et al. the Apgar score can be considered superior to the umbilical artery pH in the assessment of the perinatal status and the prediction of mortality (50).

When evaluating the weight for gestational age we did not find a correlation between the two studied groups. There was no statistically significant difference in the percentage of

children that were appropriate for gestational age, although there were more children large for gestational age in the Early Term group, and more children small for gestational age in the Late Preterm group. The weight for gestational has been shown to be an important factor influencing the outcome and mortality of newborns. Pulver et al. demonstrated that small for gestational age infants had a higher risk of neonatal and infant mortality (12). This applied to essentially all gestational ages but was especially apparent in infants born in the Late Preterm as well as in the Early Term periods. In Late Preterm infants, being large for gestational age was also a risk factor for increased mortality, while in term infants no difference between AGA and LGA infants and mortality was observed. Since in our study there was no significant difference between the two groups regarding the weight for gestational age categories we cannot notice a difference in perinatal outcome with this variable.

Identifying possible differences or equalities in perinatal outcomes could give us impulses to optimizing the management of late preterm and especially of early term neonates and it can be taken as an indication to reevaluate the standards of care for children born before 39 weeks.

The difference of the result of our study compared to the results of previous studies (13,55) could be explained by the smaller sample number of our study. Still, further research is necessary to identify the parameters that most strongly affect the perinatal outcome and how they differ in regard to gestational age, so that medical professionals are able to make informed decisions about timing of elective deliveries and provide optimal care for the newborns.

6. CONCLUSION

1. We found that the expected differences are not universally observed in all included parameters. Parity, weight, length, and Apgar score were the parameters where a worse outcome in Late Preterm births was observable, while the parameters age of the mother, umbilical artery pH, mode of delivery, and weight for gestational age did not show differences in outcomes between the two groups.
2. The most surprising finding was the insignificant difference in umbilical artery pH values, since this measure is a widely accepted tool of evaluating the perinatal outcome. At the same time, we found a higher incidence of lower Apgar scores in Late Preterm births and in light of the presence of opinions that Apgar scores are a more reliable measure of perinatal morbidity and mortality this finding could be considered to be of higher consequence
3. Thus, a tendency towards a worse perinatal outcome of late preterm births could be described, since whenever there was a significant difference observed it was associated with worse outcomes in the Late Preterm group.

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8. SUMMARY

Objectives: The aim of our study was to analyze if there is a difference in perinatal outcome between pregnancies with Late Preterm Birth and those with Early Term Birth.

Materials and Methods: Our study was conducted in the Department of Obstetrics and Gynecology of the University Hospital Split (KBC Split) of the University of Split, School of Medicine; Observed variables were age of mother in years, parity of mother, pregnancy duration in completed weeks, weight of neonate in grams, length of neonate in cm, Apgar Score (0-3; 4-7; 8-10), delivery mode (Vaginal or Cesarean Section), and size of the neonate in relation to gestational age (SGA, AGA, LGA); for statistical analysis of the data Student's t-Test was applied for numeric and normally distributed variables, and Mann-Whitney U test for numeric variables without normal distribution. For non-numeric variables Pearson Chi square test was used and alternatively Fisher exact test. The significance level was set at $P < 0.05$.

Results: We found no statistically significant difference between the two groups for the variables age and pH ($P = 0.987$ and $P = 0.377$ respectively); for the variables parity, weight, and length we did find results with a statistical significant difference between the groups ($P = <0.020$, $P = <0.001$, $P = <0.001$). Regarding the delivery mode, we did not observe any statistically significant difference between the two studied groups ($P = 0.170$), but we did find a statistically significant difference regarding the Apgar scores ($P < 0.001$) between the two groups. For the size for gestational age, in both studied groups the majority of infants were appropriate for gestational age (AGA). After using Chi-square test we found that there is no statistically relevant difference in the values of sizes for gestational ages between the two groups ($P = 0.447$).

Conclusion: The perinatal outcome of Late Preterm births and Early Term births does not differ significantly, since in just as many parameters there was no significant difference between the two groups as where there was a difference. A tendency towards a worse perinatal outcome of late preterm births could be described, since whenever there was a significant difference observed it was associated with worse outcomes in the Late Preterm group, especially when looking at the Apgar scores.

9. CROATIAN SUMMARY

Naslov: Razlika u perinatalnom ishodu između trudnoća s kasnim prijevremenim porođajem I trudnoća s ranim porođajem

Ciljevi: Cilj našeg istraživanja bio je ispitati postoji li razlika u perinatalnom ishodu između trudnoća s kasnim prijevremenim porođajem i trudnoća s ranim porođajem.

Materijali i metode: Naše istraživanje provedeno je na Zavodu za ginekologiju i opstetriciju Sveučilišne bolnice Split (KBC Split) Sveučilišta u Splitu. Promatrane varijable bile su dob majke, paritet majki, trajanje trudnoće u navršenim tjednima, težina novorođenčeta u gramima, dužina novorođenčeta u centimetrima, Apgar test (03; 4-7; 8-10), način porođaja (vaginalno ili carski rez) te veličina novorođenčeta u odnosu na gestacijsku dob (SGA, AGA, LGA); za statističku analizu podataka upotrijebljeni su Students t-test za brojčane i normalno zastupljene varijable te Mann-Whitney U-test za brojčane varijable bez normalne raspodjele. Za nebrojčane varijable korišten je Pearson Chi-kvadrat test, a kao alternativa Fisherov egzaktni test. Utvrđena razina značajnosti iznosila je $P < 0,05$.

Rezultati: Za varijable dobi i pH ($P = 0,987$ odnosno $P = 0,377$) nismo utvrdili statistički značajnu razliku između dviju skupina; za varijable pariteta, težine i dužine utvrdili smo statistički značajne razlike između skupina ($P = <0,20$, $P = <0,001$, $P = <0,001$). Kad je riječ o načinu porođaja, nismo uočili statistički značajnu razliku između dviju promatranih skupina ($P = 0,170$), međutim, utvrdili smo statistički značajnu razliku između dviju skupina u pogledu Apgar testa ($P < 0,001$). Kad je riječ o gestacijskoj dobi, većina novorođenčadi u objema promatranim skupinama bila je u skladu s gestacijskom dobi (AGA). Nakon primjene Chi-kvadrat testa utvrdili smo da između dviju skupina ne postoji statistički značajna razlika u vrijednostima veličine za gestacijsku dob ($P = 0,447$).

Zaključci: Između perinatalnog ishoda trudnoća s kasnim prijevremenim porođajem i trudnoća s ranim porođajem ne postoje značajne razlike s obzirom na to da je broj parametara u kojima nije uočena značajna razlika i onih u kojima jest jednak. Kod kasnog prijevremenog porođaja može se primijetiti tendencija prema lošijem perinatalnom ishodu jer je svaka uočena značajna razlika bila povezana s lošijim ishodom u skupini s kasnim prijevremenim porođajem, osobito ako se uzme u obzir Apgar test.

10. CURRICULUM VITAE

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