

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL**

DOCTORAL DISSERTATION

PREMATURE BIRTH

**CURRENT ETIOPATHOGENIC CONSIDERATIONS,
OF CONDUCT AT BIRTH AND POSTPARTUM
FOR PREMATURE FOETUSES**

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Premature birth. current etiopathogenic considerations, of conduct at birth and postpartum for premature foetuses

ABSTRACT

Premature birth continues to be one of the most important challenges of modern obstetrics, through its high incidence, but also because of its implications on neonatal morbidity and mortality. The consequences of prematurity are not only medical, but also social and economical, having a negative impact on the families involved. Premature infants require special medical care, efforts which are significantly higher than those implied by the care of the term infants.

The paper is structured in two parts: general and special. The first part, the general one, presents theoretical data about premature birth: its incidence, current etiopathogenic considerations and regarding therapeutic conduct, and about the premature infant: general consideration, morpho-physiological and pathophysiological particularities for the care of the premature newborn, morbidity, prognosis and causes of death of the premature infant.

The second part of the thesis, the special one, includes the personal contribution represented by a clinical trial over a period of 5 years, 2008-2012, of prematurity in the maternity of the County Emergency Hospital Craiova, insisting on premature birth, incidence – of the total of 16,083 births in period under study, 2,161 births were premature - the etiopathogenic, psychobehavioural factors involved in premature birth, the morbidity and mortality of premature infants.

The structural characteristics of premature infants are associated with increased risk of perinatal asphyxia, respiratory distress syndrome, patent ductus arteriosus, hyperbilirubinemia, hypoglycaemia, hypothermia, sepsis, compared with term infants.

I also studied the incidence of prematurity and of the risks of morbidity and mortality of the premature infants derived from twin pregnancies, the prevalence and perinatal factors associated with an increased incidence of retinopathy of prematurity, maternal infectious factors involved in preterm birth and those involved in intracranial hemorrhage of the premature infants.

In conclusion, following the study conducted, groups at risk can be established among pregnant women requiring special prenatal follow-up and preventive therapies to reduce the number of premature births. The study also showed the need to establish special therapy at birth and postpartum for premature newborns, in compliance with current standards of perinatal care, in order to reduce neonatal morbidity and mortality.

Keywords: *premature birth, premature infant, morbidity, mortality*

GENERAL PART

PREMATURE BIRTH. PREMATURE INFANT

Premature birth continues to be one of the most important challenges of obstetrics, through its high incidence, but also because of the medico-social, cultural, familial and demographic impact. Similarly, the child born prematurely, especially the small premature infant, is one of the great trials of neonatology, even when the way in which premature infants are cared for, with the introduction of modern technologies and equipment. Premature birth is a major public health problem, associated with increased neonatal morbidity and mortality.

Premature birth, according to the World Health Organization, is the birth occurring before 37 completed weeks of gestation or less than 259 days from the first day of the last menstrual period, so premature birth is a clinical obstetrical entity which occurs by the intempestive interruption of the normal course of the pregnancy, resulting in a premature infant with signs of immaturity. According to WHO, the premature infant is a baby born alive before 37 weeks of gestation, at less than 259 days, calculated from the first day of the last menstrual period.

The product of conception typically weighs less than 2,500 g, is viable, and the length is of 35 to 47 cm. Morpho-functionally, biologically, neurologically and metabolically, it is immature, not fully developed and most frequently shows a difficult adaptation to life outside the womb, requiring special care at birth and postpartum. The premature infant may frequently suffer, in the short term, from hypoglycemia, respiratory distress, apnea, temperature instability, digestive disorders: jaundice or enteral feeding difficulties, the risk of death is much higher than for a newborn at term. In the long run, complications due to prematurity can be serious: increased susceptibility to infections, especially respiratory tract infections, asthma, hypertension, myopia, deafness, growth retardation in stature-weight, neurological problems, such as paralysis or cerebral atrophy, increased risk of autism (especially in the case of the late premature).

The mechanisms that trigger premature birth do not differ fundamentally from those which trigger on term physiological birth, as the immuno-endocrine system of the pregnancy is involved, especially the maternal HPA axis, foetal and choriodecidual. They are physiological mechanisms triggered in pathological conditions as a defensive reaction and to reduce the biological cost of the aggression on the maternal-foetal functional unit.

The etiology of preterm birth is complex and multifactorial and not completely understood yet. In the presence of the most modern diagnostic tools, etiopathogenic factors of prematurity can be identified in up to 75% of cases. Their detection is very important in order to establish preventive measures.

The causes and contributing factors can be divided into two large categories: maternal (local and general) and ovular, plus epidemiological risk factors (extreme ages of pregnant women - mothers aged under 16 or over 45 years - height below 145 cm, weighing less than 45 kg before pregnancy, low socioeconomic level, excessive physical effort, gynaecological and obstetric history - within less than a year after a previous birth, a history of premature births, history of repeated miscarriages or

abortions, menstrual age less than two years), added psychobehavioral risk factors (lack of medical attention, weight gain less than 5 kg during pregnancy, labile mental state during pregnancy, smoking, alcohol, drugs, caffeine, occupational poisoning with lead, mercury, excessive sexual activity in the last trimester of pregnancy).

The therapeutic conduct in premature birth

- Prevention of premature births requires knowledge of etiologic factors and initiation of measures that mitigate risk factors during preconception and continuing in the prenatal period. In addition, special attention is given to pregnant women during pregnancy regarding nutrition, occupational health, psycho-educational factors, pathologies of pregnancy.
- Premature birth risk score allows prospective study of each pregnant woman under surveillance and initiating remedial measures in cases in which there is an increased risk above a certain level. The best known is the risk factor coefficient for premature birth which Papiernik introduced;
- The measurement via ultrasound of the cervix length is a predictive factor in the determinism of premature birth;
- Obstetrical conduct in premature labour: bed rest, lifestyle modification and reduction of physical effort, tocolytic therapy and hormone replacement therapy, cervical cerclage, corticosteroids, antibiotics.

The pathophysiological characteristics of prematurely born babies, due to the immaturity of all organs and systems, explain the difficulty in adapting to life outside the womb, and there are multiple risks of respiratory distress, hypothermia, electrolyte disturbances, increased susceptibility to infection, risk of intracranial hemorrhage.

The care of the premature newborn implies: stabilization of the premature newborn, ensuring and maintaining heat, maintain breathing, prevention of infections and proper nutrition.

The complications of prematurity are: respiratory distress syndrome, pulmonary bronchodysplasia, cerebral complications (ICH), cardiac complications (PDA), anaemia of prematurity, hemorrhagic syndrome, infections, digestive complications (UEN), jaundice of prematurity, hypoglycaemia, hypothermia, hearing disorders and retinopathy of prematurity.

The prognosis is significantly influenced by birth weight and especially gestational age, depending on the cause of the spontaneous premature birth, the most harmful being acute and chronic infections, poisonings of the mother and pregnancy pathologies. Finally, it depends on the quality of the care provided during the first hours after birth. Extreme prematurity, birth stress, intrapartum asphyxia worsen the prognosis.

Prematurity is about half of the neonatal mortality and nearly 80% of mortality in the first 10 days of life. The late prognosis can be encumbered by sequelae, more or less serious.

The main causes of mortality in preterm infants are hypoxia, intraventricular hemorrhage, respiratory distress syndrome, infections, congenital malformations, blood dyscrasias.

The increased risk of death of the premature infants, compared to term infants is maintained during the first year of life as well, being 2.1 to 5.1 times higher and it is mainly due to the association with congenital malformations.

SPECIAL PART

Justification

Prematurity is one of the obstetric entities whose consequences are among the most complex and powerful. Preterm delivery complicates a significant percentage of pregnancies (5-15%), with different variations from country to country, and it is the main cause of perinatal morbidity and mortality worldwide. Premature infants, especially those with very low birth weight, incumbent over 50% of neonatal deaths which recognize causes other than congenital malformations.

Purpose of the study

In the study conducted I planned to make an assessment of the etiopathogenic factors, especially psychobehavioral ones, involved in premature birth, on a group of 200 patients, apparently healthy primiparous women, making a comparison between a study group made up of 100 patients who delivered prematurely and another batch of 100 patients - control group, who delivered at term. Another purpose of the study was the careful analysis of the premature newborns, their morbidity and mortality.

Objectives of the study

- Identifying factors that may cause the removal of psycho-behavioral pathology in the determinism of preterm birth.
- Identifying the differences between mothers who gave birth to premature infants and those who gave birth to normal weight babies. These differences are related to the presence of etiopathogenic factors of prematurity in the case of patients who gave birth prematurely.
- Identifying the measures which can lead to the removal of the etiological factors of premature birth.
- Evaluating the consequences of triggering premature birth on the newborn infant.
- Evaluation of the implementation of health policies aimed at protecting pregnant women against the increasing incidence of psycho-behavioural factors, thus avoiding the risk of premature birth.
- Establishment of special therapy, at birth and postpartum of premature newborns, in compliance with current standards of care perinatal to reduce morbidity and mortality of premature infants.

Methods and stages of work

For the purpose of my project I conducted a retrospective study of births over a 5 year period, January 2008 - December 2012, conducted in the Obstetrics and Gynaecology Department of the Emergency County Hospital Craiova, given all births that took place in this period, insisting on premature births. I included in the study data about both the mothers as well as the newborns. During the time that this study reported there have been a number of 16,083 births, of which 2,161 were premature births, 164 twin births, 171 preterm infants with birth weight <1000 g.

The study method involved a comparative tracking, over a period of 5 years, of the premature births and those on term, of the etiopathogenic factors involved in preterm labour, morbidity and mortality of premature newborns compared with those of the newborns with normal weight. I also studied the involvement of maternal infectious pathology in the premature birth, the risk factors involved in intracranial hemorrhage of the premature infants, the risks of prematurity in twin pregnancies, but also the evaluation of the prevalence and risk factors associated with retinopathy of prematurity.

This study was conducted on the basis of the elements drawn from the observation sheets of the mothers who gave birth in the clini, as well as from the medical records of the newborns.

In relation to prematurity, I studied several variables related to the mothers, the birth and the newborn infant.

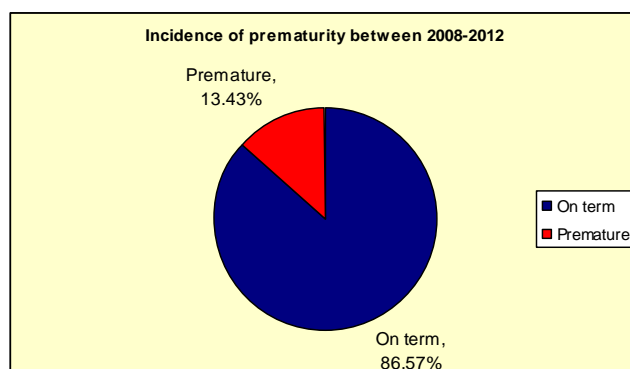
The information collected was entered into a computer database and the results were processed, including a statistical processing of the information collected and their graphic representation.

RESULTS AND DISCUSSIONS

The incidence of prematurity in 2008-2012

Distribution by years of total births and premature births

Year	Total number of births	Premature births	Incidence
2008	3.221	392	12,17%
2009	3.397	425	12,51%
2010	3.415	498	14,50%
2011	3.106	456	13,35%
2012	2.944	390	13,24%



Of the total of 16,083 births in the period studied, 2161 were premature births, i.e. 13.43%.

I have not observed a significant variability in the percentage of premature pregnancies in the five years analyzed, as demonstrated by applying the Chi-square test, whose result, $p = 0.998$, was much higher than the maximum allowed value for a significant difference in statistical terms, 0.05.

Despite the remarkable progress achieved in the field of obstetrics and neonatology, the incidence of prematurity remains high. The explanation for this lies in the fact that women resort more frequently to the techniques for assisted human reproduction: in vitro fertilization or artificial insemination (cervical or uterine fertilization), thus achieving multiple pregnancies, in the increased age of the mothers (late maternity), to which psychobehavioral risk factors can also be added: maternal drug consumption, smoking during pregnancy, maternal stress, sustained physical effort. The etiological factors yet unknown should not be neglected either.

It should also be taken into account that the survey was conducted in the maternity of the Emergency County Hospital Craiova, which is a Level 3 unit, the only one with this degree in all of the Oltenia region, thus all the problematic cases, especially the premature births, are directed to this hospital unit.

Evaluation of etiopathogenic, psychological and behavioural factors involved in preterm birth

Etiopathogenic factors	Women who gave birth prematurely	Women who gave birth to normal weight babies
1. Age - under 18 years old - 18 - 35 years old - over 35 years old	47% 19% 34%	17% 62% 21%
2. Environment of origin - rural - urban	79% 21%	37% 63%
3. Profession - housewives - employed	70% 30%	28% 72%
4. Degree of education - uneducated - educated	65% 35%	41% 59%
5. Marital status - married - single	40% 60%	65% 35%
6. Monitoring of pregnancy - < 5 consultations - ≥ 5 consultations	74% 26%	43% 57%
7. Menstrual age - < 3 years - ≥ 3 years	78% 22%	12% 88%
8. Weight gain during the pregnancy - < 5 kg - 5 ÷ 12 kg - ≥ 12 kg	51% 39% 10%	0% 65% 35%
9. Smoking - smokers - non smokers	77% 23%	28% 72%
10. Alcohol - drinkers - non drinkers	10% 90%	4% 96%
11. Physical work - subjected to physical work - protected	80% 20%	33% 67%
12. Number of abortions - < 2 abortions - ≥ 2 abortions	32% 68%	74% 26%

Morbidity and mortality of premature infants compared to those of term newborns

Of the 2,161 preterm infants, 171 (7.91%) are preterm newborns with extremely low birth weight, i.e. less than 1,000 g.

Incidence of extreme prematurity complications compared with other preterm newborns, respectively normal weight infants

Morbidity	171 prematures with BW < 1.000g	171 prematures with BW ≥ 1.000g	171 normal weight newborns	p square Chi
Perinatal hypoxia Apgar Score at 1, respectively 5 minutes, <5	124 (72,51 %)	38 (22,22 %)	8 (4,67%)	2.78 x 10 ⁻⁴²
Respiratory distress syndrome (RDS)	110 (64.32 %)	46 (26,9 %)	13 (7,6 %)	1.09 x 10 ⁻²⁸
Intraventricular hemorrhage	100 (58,47 %)	60 (35,08 %)	5 (2,92 %)	3.30 x 10 ⁻²⁷
Pulmonary hemorrhage	116 (67,83 %)	34 (19,88 %)	2 (1,17 %)	7.71 x 10 ⁻⁴³
Crises of apnoea	101 (59,06 %)	33 (19,29 %)	1 (0,58 %)	6.93 x 10 ⁻³⁵
Hypoglycaemia	64 (37,42 %)	41(23,97 %)	15(8,77 %)	3.04 x 10 ⁻⁹
Disorders of the acid-base balance Changes in blood gases	112 (65.49 %)	59 (34,5 %)	12 (7,01 %)	1.98 x 10 ⁻²⁸
Convulsions	30 (17,54 %)	12 (7,01 %)	3 (1,75 %)	1.00 x 10 ⁻⁶
Infections	113 (66,08 %)	56 (32,74 %)	17 (9,94 %)	2.42 x 10 ⁻²⁶
Retinopathy of prematurity (ROP)	50 (29,23 %)	25 (14,61 %)	0 %	1.92 x 10 ⁻¹³
Bronchopulmonary Dysplasia (BPD)	119 (69,59 %)	7 (4,09 %)	1 (0,58 %)	5.93 x 10 ⁻⁶¹
Necrotizing enterocolitis (NEC)	12 (7,01 %)	4 (2,33 %)	1 (0,58 %)	2.73 x 10 ⁻⁴

For the various comorbidities identified in the three groups, all results obtained by the Chi square test were far lower than 0,001; therefore, we can state that the group of preterm infants with BW <1000g suffer significantly higher from the various comorbidities compared to the group of preterm newborns with BW > 1000 g, which in turn is highly and significantly more affected by various comorbidities than the normal weight group.

Mortality of extreme prematurity, compared to that found for other groups of preterm or normal weight newborns

Mortality	171 premature infants with BW < 1.000g	171 premature infants with BW ≥ 1.000 g	171 normal weight infants
Deaths	70 (40,94 %)	16 (9,36 %)	1 (0,58 %)

Neonatal mortality of the premature newborn, as well as in my study, is significantly higher compared to that of newborns at term. The greatest risk of mortality belongs to extreme prematurity, the same category of preterm infants also suffering from the most comorbidities.

Implications of urinary infection during pregnancy on the newborn

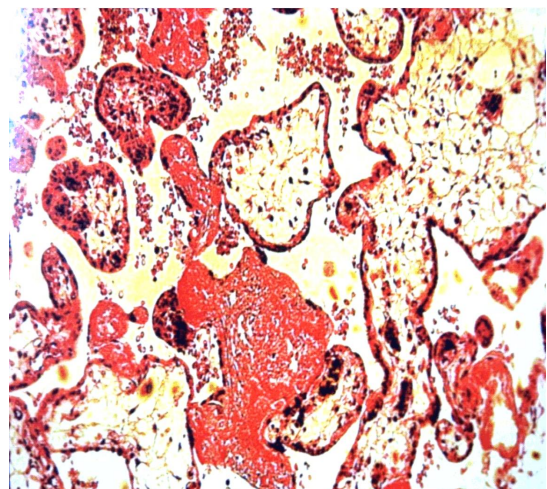
	768 newborns from mothers with urinary infection	768 newborns from mothers without urinary infection	p Chi square
Apgar Score ≤ 7 at 5 minutes	599 (77,99%)	133 (14,32%)	<0,001
Incidence of prematurity	399 (51,95%)	56 (7,29%)	<0,001
Neonatal infectious complications	198 (25,78%)	49 (6,38%)	<0,001
RDS	92 (11,98%)	36 (4,69%)	<0,001
Perinatal mortality	31 (4,04%)	9 (1,17%)	<0,001

Etiopathogenic, clinical, histopathological issues regarding the involvement of dental infectious outbreaks in premature birth

Our study using, clinical examination, ultrasounds, bacteriological examinations of amniotic fluid in the placenta as well as histopathological examinations, showed the subclinical development of chorioamnionitis. The chorioamnionitis inflammatory process, by the high synthesis of interleukins and local prostaglandins, prompted uterine contractions (on the 1,344 pregnant women who gave birth prematurely), accounting for premature birth (14%).



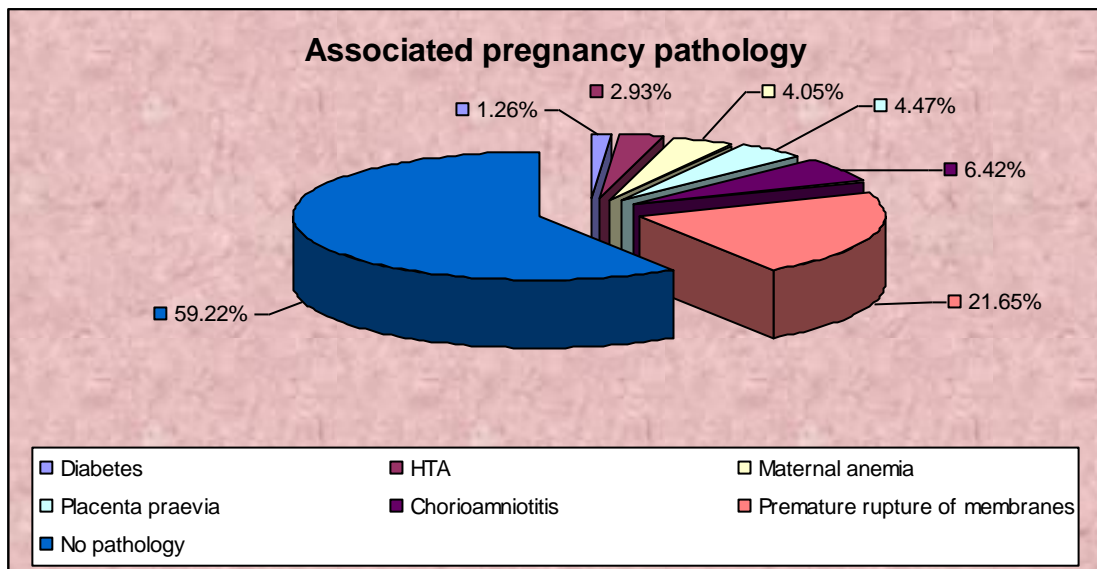
Overview of foetal membranes in the infection of the amniotic sack. Massive inflammatory infiltrate. Coloration HE, x100.



Placenta at 36 weeks gestational age with chorioamnionitis. Areas of trophoblastic necrosis obstructing the vessels. Coloration HE, x100.

Risk factors involved in intracranial hemorrhage in premature infants

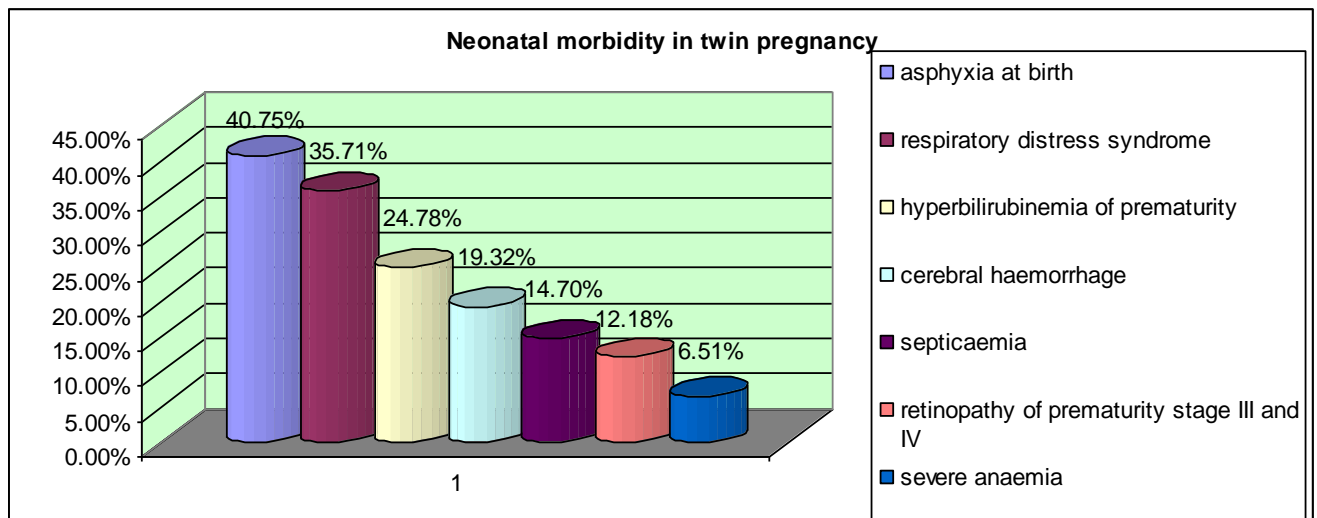
In the cases studied the pathology of pregnancy was present in 294 patients (41%): premature rupture of membranes (155 cases), chorioamnionitis (46 cases), placenta praevia (32 cases), maternal anaemia (29 cases), hypertension (21), maternal diabetes (9 cases).



Risks of prematurity in twin pregnancy

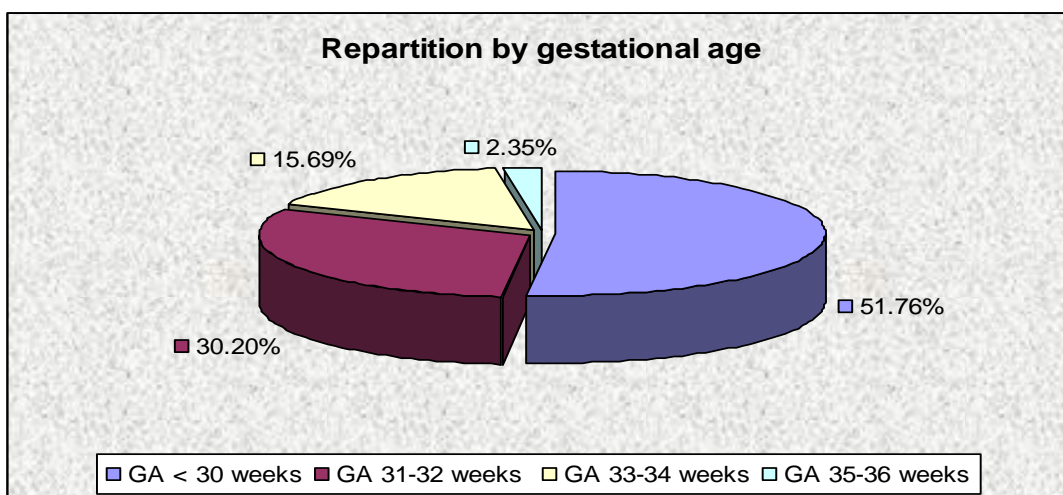
Of the 16,083 births in the period studied, 164 were twin pregnancies, i.e. 1.019% . The variation from year to year is not statistically significant (Chi square = 0.983 $p > 0.05$).

Of the 328 twins, 201 (61.5%) were born prematurely, meaning that the incidence of prematurity in twin pregnancies is approximately 5-6 times higher than prematurity in single pregnancy (where it is of 10-12% of all births).



Retinopathy of prematurity - prevalence, risk factors associated perinatal

716 preterm infants were included in the study, who underwent eye screening. Of these, 255 had retinopathy at different stages (35.61% - a percentage similar to that of literature). Many of them had Stage I and II retinopathy without "plus factor", which regressed spontaneously without treatment, only 19 preterm infants requiring laser treatment performed at I.O.M.C. Bucharest.

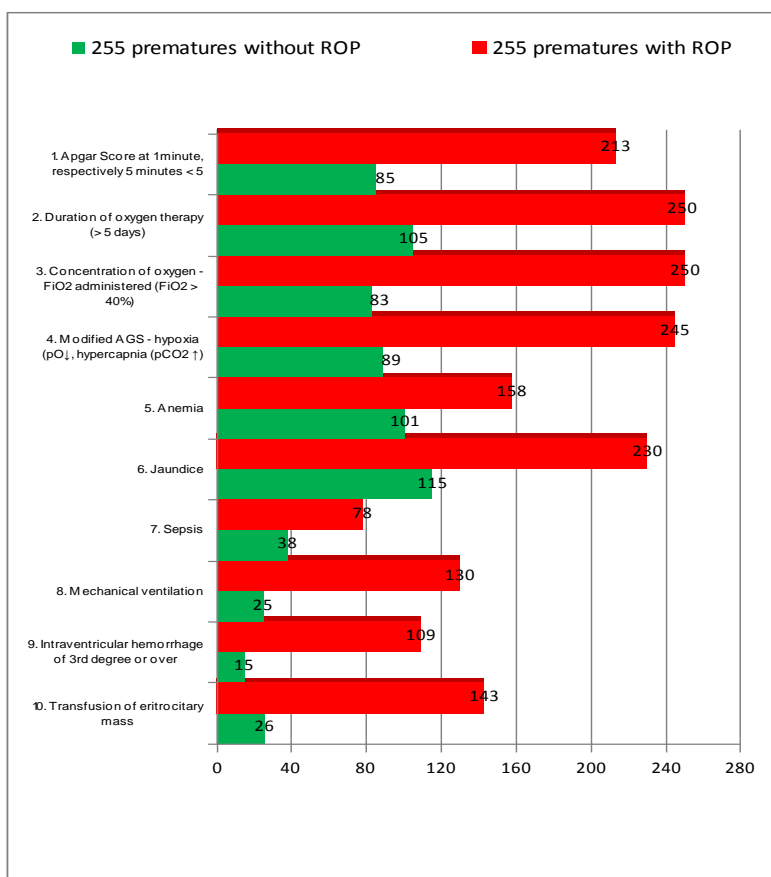


ROP incidence increases in direct proportion with the decrease of the gestational age, below 30 weeks being the most cases - 132 preterm newborns, more than half of all cases of ROP detected in the 5 years in the studied group.

Risk factors related to the mother, involved in the onset of ROP:

Risk factors involved in the onset of ROP related to the mother	255 premature infants with ROP	255 premature infants without ROP
1. Lack of medical attention	59 (23,13%)	26 (10,19%)
2. Premature rupture of membranes	108 (42,35%)	57 (22,35%)
3. Diabetes	29 (11,37%)	8 (3,13%)
4. Hypertension	54 (21,17%)	19 (7,45%)

Perinatal factors associated with prematurity significantly increase the incidence of retinopathy: perinatal hypoxia (manifested by low Apgar score at 1 minute, respectively 5 minutes, confirmed by changes in blood gases), duration of oxygen therapy, increased oxygen concentration, acid-base imbalances, anaemia, jaundice, sepsis, mechanical ventilation, intraventricular hemorrhage, repeated transfusions.



Conclusions:

- The first conclusion is that the incidence of prematurity remains high, despite the remarkable progress achieved in the field of obstetrics and neonatology, since mothers increasingly resort to assisted human reproduction techniques, the increase of the maternal age, to which the psycho-behavioral risk factors are added.
- Risk groups can be established among pregnant women (extreme ages, origin, profession, marital status, smoking, alcohol, etc.), which make them eligible for special prenatal monitoring and prophylactic treatment.
- Premature babies have an increased morbidity and mortality, the percentage being higher as the gestational age is lower, preterm infants being physiologically and metabolically immature compared to normal weight newborns.
- Maternal urinary infections adversely affect the foetal condition, ranging from minor damage to severe complications, even death. Diagnosis and treatment are necessary for the urinary tract infections of the mother during pregnancy.
- The bacterial flora in the dental plaque, by determining septic dentate outbreaks and bacteraemia, causes uteroplacental septic foci and often premature birth and foetal hypotrophy.
- Chorioamnionitis evolves often with a low profile symptomatology or is asymptomatic, but it affects the foetus, which can evolve with growth restriction
- Histopathological examinations of the placenta and amniotic membranes which demonstrate the presence of chorioamnionitis, even in the absence of clinical symptoms, are strong elements involving disease in foetal hypotrophy and preterm birth.
- is necessary to avoid risk factors associated with intracranial hemorrhage, perinatal hypoxia, infections, convulsions, mechanical ventilation as well as pathology of pregnancy: premature rupture of membranes, chorioamnionitis, placenta praevia, maternal anaemia, hypertension, diabetes of the mother, because once ICH is installed, the therapeutic means are reduced and very inefficient, and the mortality and potential neurological and psychomotor sequelae in the long term are significant.
- Twin pregnancy is largely encumbered by risk factors: prematurity, late eclamptic, placenta praevia, dystocic presentations, premature rupture of membranes, anaemia.
- Twin pregnancies have a higher rate of premature birth compared to single foetus pregnancies; because of this, rules of therapeutic conduct are necessary in the case of twin pregnancies, in order to prevent preterm birth.
- Neonates from twin pregnancies constitute a distinct category as a result of these risks (birth asphyxia, respiratory distress syndrome, hyperbilirubinemia, brain hemorrhage, sepsis, retinopathy of prematurity, anaemia, increased mortality) requiring special follow-up during antenatal, neonatal and postnatal care.
- Statistically, but also consistent with the literature, we note a greater hazard to the second twin, for which the perinatal morbidity and mortality are significantly higher than for the first foetuses. This is mainly due to perinatal asphyxia and mechanical trauma caused by obstetrical vaginal manoeuvres. We believe that caesarean section should become an indication in order to protect the second foetus, thereby restricting vaginal manoeuvres.
- Premature babies with low birth weight and low gestational age have an increased risk of developing retinopathy of prematurity. Premature infants included in the study who presented ROP had predominant weight under 1500 g and the age below 32 weeks of gestation.
- To prevent the risk of premature birth and reduce long-term negative consequences for premature infants, a multidisciplinary collaboration is imperative (obstetrician, neonatologist, neurologist, psychologist and family) and imposing compliance with the standards of perinatal care.

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