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”CAROL DAVILA”, BUCHAREST

NEONATOLOGY

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**NEWBORNS FROM TWIN PREGNANCY - COMPARATIVE CLINICAL STUDY
ON THE MANAGEMENT OF POSTNATAL COMPLICATIONS**

DOCTORAL THESIS SUMMARY

Thesis Supervisor:

PROFESSOR VLĂDĂREANU SIMONA, PhD

Ph.D.Candidate:

MĂREȘESCU (PREDESCU) ANA-MARIA

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INTRODUCTION

This research project comes to complete a period of about four years of discovery, research and a lot of work.

Defined under the title: *'Newborns from twin pregnancy - comparative clinical study on the management of postnatal complications'* it was born out of a passion to study twins.

From the very first day of pregnancy, the mother/twin triad may constitute the subject of various scientific works because the objective is focused on three beings, the mother and the twins, who although they form and develop in a simultaneous manner, have different traits and characteristics that require individual approaches from a medical point of view. Since intrauterine life, a special bond is created between the mother and the twins, subject to change, transformation and which becomes permanent.

In this paper my purpose was to address a variety of issues related to postnatal complications arising in twins as well as the need for adequate management of this category of patients.

The pathology specific to twins has presented over time and still presents a great interest in scientific research, both due to the psycho-emotional implications and the consequences on the quality of life, arising not in a new-born but in two new-borns simultaneously.

Thus, the research becomes essential to know the principles underlying postnatal complications in this category of new-borns.

From the point of view of the content, the paper is structured in two parts: the first part or the current stage of knowledge, in which we reviewed the latest information on the management of complications in new-born twins, and the second part, includes the actual clinical study, discussions and conclusions.

PART I.

CURRENT STATE OF KNOWLEDGE

PREGNANT WITH TWIN PREGNANCY

This chapter is a review of the latest information about twin pregnancy, the possible complications that may occur in the case of a twin pregnancy, as well as the management of these complications during the neonatal period.

The antenatal complications identified in the pregnant woman with twin pregnancy studied were: arterial hypertension, gestational diabetes, premature rupture of membranes, anaemia and infections. Complications associated with the time of birth, anaesthesia options, as well as the choice of the mode of birth are the topic of chapter 1.

Certainly, these complications occurred in the pregnant woman with twin pregnancy with direct or no influence on the new-borns led to the optimization of the management of neonatal complications.

Twin pregnancy is a pregnancy at risk for both new-borns and the mother whether it is obtained naturally or through in vitro fertilization.

Neonatal complications arising from twin pregnancies obtained by in vitro fertilization are found to the same extent in twin pregnancies obtained spontaneously, and the percentage of birth by caesarean section was relatively equal in both categories.

In the case of twin pregnancy, the amnionicity and foetal presentation at the onset of labour influence the choice of mode of birth: by vaginal route or by caesarean section. [30]

Antenatal corticoid prophylaxis in pregnant women with twin pregnancies at risk of premature birth is one of the most effective perinatal strategies to improve neonatal outcomes, as well as reducing the incidence and severity of respiratory distress syndrome and mortality in new-borns.[28][27]

Corticosteroids administered prenatally at levels that mimic physiological stress cause foetal lung maturation by increasing the activity of enzymes responsible for surfactant biosynthesis, resulting in improved lung compliance.[22],[28]

The increased incidence of twin pregnancies reveals new and serious medical and ethical problems for both parents and doctors.

NEWBORNS FROM TWIN PREGNANCY

New-borns from twin pregnancy are associated with a number of complications associated with multiple pregnancy. The most common complication in new-borns from twin pregnancy is prematurity, which plays an important role in both mortality and short-and long-term morbidity associated with this category of new-borns.

Although the transition from intrauterine to ectopic life is complex, most new-borns do not require resuscitation at birth and admission to the neonatal intensive care unit.

Accurate risk assessment strategies, complications, and proper management of twin new-borns can reduce the growing need for neonatal intensive care by improving long-term outcomes.[44]

For new-borns from twin pregnancies, especially for those who need intervention at birth, actions taken during the first minute after birth, the so-called "golden minute", can have important implications for long-term results.[42]

Twins are often admitted to neonatal intensive care, and this is because they tend to be born earlier and have much less weight compared to new-borns from single pregnancy. The chances of premature birth and admission to neonatal intensive care increase with each child in a pregnancy as well as the type of twin pregnancy (mono/mono, mono/di, di/di).

In this paper we studied the short-term neonatal complications that appeared immediately after birth: respiratory distress syndrome, neonatal transient tachypnoea, metabolic disorders, hypotension, apnoea with serious consequences on the evolution of new-borns.

For dichorionic twins, the recommendations of the American College of Obstetricians and Gynaecologists (ACOG) are to delay the clamping of the umbilical cord for at least 30 to 60 seconds after birth, in vigorous new-borns, even premature.[31] Monochorionic twins are not suitable candidates for delayed umbilical cord clamping.

The management of new-born care is individualized according to the presence or absence of complications, and each twin must be assessed individually to see whether or not it requires admission to the neonatal intensive care unit.

PART II.

PERSONAL CONTRIBUTIONS

MOTIVATION, WORKING HYPOTHESIS AND OBJECTIVES OF THE STUDY

The motivation for choosing this PhD topic is related to the chosen specialty, Neonatology, and this project is due to my personal curiosity for twins as well as the desire to deepen and identify as early as possible the complications that can occur in twins. The possibility of identifying as early as possible the complications that may occur in new-borns make the difference between life and death. Even though the number of twin pregnancies is lower than single pregnancies, complications that can occur in this category of new-borns are quite common due to premature birth. Most of the time, not identifying in time the complications may endanger the life of a new-born and lead to his / her admission to TINN. The design of this paper started from the idea that the two twins can be compared, based on the identification and comparison of complications that occur in one or both new-born twins. So, the goal setting was very clear.

- ***Main objectives***

- Identification of complications in IVF-obtained twins compared to naturally obtained twins relative to the gestational age
- Identifying complications in twin 1 compared to twin 2

- ***Secondary objectives***

- The importance of delayed clamping in new-born twins
- The importance of antenatal corticosteroid therapy to prevent complications in twins

The purpose of the paper was to obtain as much data as possible about postnatal complications arising in new-borns from twin pregnancy. The study was also based on the implications for each individual who was born as part of a pair.

The data obtained in this studio will allow a better understanding of the monitoring and management needs of twin one compared to twin two and twins obtained by in vitro fertilization versus twins obtained naturally.

MATERIAL AND STATISTICAL METHODS USED

The next step consisted in the preparation of the material and the choice of the statistical method necessary in carrying out this study. This study was carried out in the clinic of Obstetrics Gynaecology and Neonatology of the Elias emergency University Hospital in Bucharest, Romania. This study included a number of 180 patients from twin pregnancy born in the clinic in the last four years, between October 2017 and October 2021.

Therefore, the total group included 90 pairs of twins, of which 40 pairs of twins came from pregnancies obtained by in vitro fertilization and 50 pairs of twins came from pregnancies obtained naturally. Patients were divided into two groups, namely: a group with twins who came from pregnancies obtained by fertilization versus twins that were obtained naturally and another group that compared twin I with twin II.

In order to carry out the statistical analysis I relied on descriptive statistics, calculating the incidence, average, and standard deviations organized in the form of synoptic tables, columns and graphs of sectoral type. To compare the results and the variables for the newborn twins we used chi-square analysis and the Student's t-test. For 2x2 contingency tables we calculated OR with 95% confidence interval. The data was processed and systematized in the Excel program of the Microsoft Office 365 suite and then transferred to the SPSS statistical program version 26.0.

To complete the Excel, we used WinStat and Xlstat "add-ins " for graphical representations and statistical analysis of data. The statistically significant result was interpreted at a p value<0.05.

RESULTS AND DISCUSSIONS

In the study period, October 2018 - October 2021, from the database a total of 180 patients (90 pairs of twins) were eligible for the study, they had an average gestational age of 35.8 s for twins obtained by in vitro fertilization and 36.1 s for twins derived from naturally obtained pregnancy. There were no significant differences in gestational age ($p=0.47$) at which the birth took place.

All new-borns were monitored by the neonatologist from birth to discharge in the Neonatology Department of Elias University Emergency Hospital.

New-borns from single pregnancy, new-borns from triple or quadruple pregnancy and new-borns from triple pregnancy reduced to twin pregnancy were excluded from the study.

Thanks to a good collaboration with colleagues from obstetrics gynaecology, in addition to the management of neonatal complications, we were able to analyse maternal complications and their influence on twin new-borns.

The average age of the twin pregnancy patient was 36 years. A statistically significantly lower average age was observed ($p=0.0001$) of patients who had a natural pregnancy compared to patients who obtained pregnancy through assisted reproduction techniques (in vitro fertilization).

The results of the study also showed that scheduled caesarean delivery and maternal complications did not influence the occurrence of neonatal complications differently than mothers who tried a natural labour and gave birth naturally. The choice of the mode of birth by caesarean section was 98 %. At the time of admission for delivery, a number of 66 pregnant women had complications: 62% of pregnant women had premature birth, 53% of pregnant women had premature rupture of membranes. Maternal anaemia was present in 14% of cases. The incidence of pregnancy-induced hypertension, preeclampsia was in the percentage of 10%. Similar to this observation, results were found in the 2018 study conducted by Tripathi M. and collaborators.[114]

The prevalence of complications in new-born twins from pregnancy obtained through in vitro fertilization was relatively similar to that of twins from pregnancy obtained naturally. Of the IVF pregnancies 57.5% new-borns were premature, while of the naturally obtained pregnancies 56% new-borns were premature. No statistically significant differences of complications were observed between preterm infants from IVF pregnancies compared to premature infants from naturally occurring pregnancies ($\chi^2 [1, N=180] = .04, p=.84$).

In several studies performed on twins conceived by in vitro fertilization, it was found that long-term complications appear to be similar to those of naturally conceived twins, even if the first ones required several days of hospitalization in neonatal intensive care.[115][116]

Some studies have shown that the risk associated with twins with weight differences is related to the increased incidence of prematurity and the restriction of growth of the smaller twin.[117][118]

This was also observed in twins obtained by assisted reproduction techniques noting that in this category of new-borns there was an increase in the incidence of prematurity and low birth weight.[119]

The vast majority of twins hospitalized in NICU (χ^2 [1, N=180] = 51.89, $p < 0.00001$), had a rapid recovery and a favourable evolution and only 84 new-borns required hospitalization for more than 5 days, having gestational age less than 37 weeks and required administration of oxygen under the cephalic tent (χ^2 [1, N=180] = 49.35, $p < 0.00001$), non-invasive mechanical ventilation of CPAP type (χ^2 [1, N=180] = 30.14, $p < 0.00001$) or (χ^2 [1, N=180] = 5.59, $p = 0.02$).

Even if some of the twins with gestational age < 37 weeks required monitoring in the neonatal intensive care unit for a period of more than 5 days as well as treatment, this category of patients evolved favourably and were transferred to the neonatology clinic to be subsequently discharged. This is not surprising and is consistent with other studies done on twins.[119],[120]

The analysis performed on the APGAR Score shows that it was not influenced at 1 minute by the way of obtaining the pregnancy ($p = 0.14$), the order of birth ($p = 0.81$), the sex of the new-born ($p = 0.53$), but it was significantly influenced by gestational age ($p = 0.0001$) and birth weight ($p = 0.0003$).

Another analysis by Jerrie S. Refuerzo and collaborators conducted a randomized control study that compared neonatal complications occurring in preterm-born twins versus full-term twins. They concluded that neonatal complications occurred especially in preterm infants and they had an eight-fold higher risk of developing respiratory complications compared to full-term new-borns, requiring admission to the neonatal intensive care unit, but where mechanical ventilation and oxygen administration was short-lived.[121]

Complications such as respiratory distress syndrome, hypoglycaemia, hypotension, and apnoea occurred more frequently among MC twins, as most cases of MC twins were born before term.

According to the present study, it seems that chorionicity does not have the importance when deciding to give birth before 37 weeks.

In the sample of patients participating in the study in which at least one complete treatment of antenatal corticoid prophylaxis (Dexamethasone) was initiated, the statistical analysis performed showed that it is beneficial in reducing short-term respiratory morbidity, i.e. respiratory distress syndrome (χ^2 [1, N=180] =5.64, p=0.02), significantly reduces surfactant administration (χ^2 [1, N=180] = 4.48, p=0.03), reduces fan support (χ^2 [1, N=180] = 3.8, p=0.05), decreases the hospitalization time (t-test = -8.45, p <0.0001) and is associated with a significant decrease in neonatal death.

Research addressing the effects of corticoid therapy in twins is limited and contradictory. Possible reasons for this situation include the fact that many of the studies conducted to date are due to the small size of the sample of new-borns.[124].[125][126]

We noticed that in case of delayed clamping, it is more likely that new-borns will not require admission to the intensive care unit for a shorter period of time (χ^2 [1, N=180] = 37.06, p<0.00001), compared to new-borns with immediate clamping, being a statistically significant correlation. Statistical analysis also showed that delayed clamping is beneficial in reducing respiratory distress syndrome, resulting in reduced surfactant administration, reduced ventilator support, and reduced neonatal admission.

We did not observe any statistically significant difference between twin I and twin II regardless of the mode of obtaining the load in terms of the need for non-invasive mechanical ventilation (p=0.6), invasive mechanical ventilation (p=0.81) as well as the administration of treatment (p=0.98).

Of the pregnancies obtained through IVF (N=80), 21 (26.25%) of new-borns had apnoea at birth, while in the pregnancies obtained naturally (n=100), 16 (16%) had apnoea at birth.

Of these, in IVF pregnancies all new-borns required caffeine administration, while in naturally obtained pregnancies only 15 (93.8%) new-borns required caffeine administration. Reduction of complications in twins may be due to good maternal antenatal monitoring, as well as prophylactic administration of corticosteroids for the management of preterm labour.

CONCLUSIONS

Taking care of the new-born twins is a real challenge for the neonatologist.

Not all neonatal complications associated with twins can be prevented, but they can be detected antenatally and subsequently intervene in a controlled manner through appropriate and prompt management in reducing morbidity and mortality.

Perinatal deaths can be minimized by avoiding premature births through combined measures performed in pregnant women such as prophylactic cervical cerclage, short-term tocolysis, but above all prophylactic antenatal administration of corticosteroids.

The diagnosis of twin pregnancy as well as the determination of chorionicity is essential for the anticipation of neonatal complications.

In this study, very few differences were observed between twin one and twin two. Given the current rate of caesarean delivery for both twins as well as the proper management of antenatal risk factors, we speculate that this could be related to standardized management protocols for twin pregnancy and birth in this clinic.

A strong point of the present study is that the sample of patients allowed to analyse the key factors (gestational age, the method of obtaining pregnancy, antenatal corticosteroid therapy, delayed clamping) and to obtain results with statistical significance.

In the sample of patients participating in the study who initiated at least one complete treatment of antenatal corticoid prophylaxis (dexamethasone) the statistical analysis performed showed that it is beneficial in reducing short-term respiratory morbidity, respiratory distress syndrome, significant reduction of surfactant administration, ventilator support, reduction of admission time and is associated with a significant decrease in neonatal death.

Antenatal corticoid prophylaxis also does not eliminate the occurrence of transient neonatal tachypnoea in term new-borns. The completion of a complete course of dexamethasone by the time of birth plays a favourable role in reducing neonatal complications.

Moreover, more robust evidence is needed to justify the efficacy of corticoid prophylaxis in the twin pregnancy patient.

At new-borns where delayed clamping was performed, this was associated with a significant benefit in terms of neonatal morbidity, especially respiratory morbidity, not influencing metabolic imbalances. I found that the practice of delayed clamping is associated

with beneficial outcomes, such as reducing neonatal complications and reducing the duration of admission of new-borns to NICU.

In order to explore the reasons and analyse delayed clamping in twins I performed several ad-hoc analyses. I anticipated that in any pair of twins, the second twin is more prone to postnatal complications and we performed delayed clamping in all new-borns where the clinical condition allowed, and the results showed that respiratory complications were less. In fact, we would have expected to see a significant difference in neonatal complications when comparing the categories of new-borns, twin one versus twin two and twins obtained by fertilization compared to twins obtained naturally, but there were no significantly satisfactory differences between the groups studied.

We cautiously interpreted the data obtained because the sample size of these subgroups was relatively small and this information was carried out as hypothesis-generating analyses. In the categories of twins studied, we found no significant differences in neonatal death before discharge and /or severe neurological damage between new-borns where delayed clamping was performed and those where it was not performed.

Further research is needed to determine whether there is a benefit in terms of mortality, morbidity in twins where delayed clamping was performed to identify the optimal duration of umbilical cord clamping in twins as well as its correlation with chorionicity. The category of twins with gestational age below 37 weeks was more prone to complications and required hospitalization for more than 5 days. Data on neurological complications in new-born twins are related to prematurity and low birth weight.

Twins from pregnancy obtained through fertilization had apnoea episodes more frequently compared to twins from pregnancy obtained naturally and required caffeine administration.

Twins represent the category of new-borns with a multitude of challenges and controversies regarding the care, approach and management of neonatal complications as outlined in this paper.

Efforts to standardize diagnostic criteria and assess new-born twins, report results, and the development of national practice guidelines will help research effectiveness and clinical practice.

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Scientific activity – published articles

1. **Predescu (Măreșescu) Ana Maria**, Prof. Dr. Radu Vlădăreanu, Simona Vlădăreanu, *Maternal and neonatal complications in spontaneous twin pregnancy versus IFV twin pregnancy*, Ginecologia.ro, Anul IX, Nr 33(3/2021), DOI: 10.26416/Gine.33.3.2021;

2. **Predescu (Măreșescu) Ana Maria**, Vlădăreanu Maria Irina, Simona Vlădăreanu, *Delayed cord clamping in newborn babies from twin pregnancy*, Ginecologia.ro, Anul IX, Nr 33(3/2021), DOI: 10.26416/Gine.33.3.2021;