

UNIVERSITY OF MEDICINE AND PHARMACY

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**Particularities of Perinatal Care for Premature Infants
Conceived by In Vitro Fertilization**

DOCTORAL THESIS ABSTRACT

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Introduction

In recent decades, in vitro fertilization (IVF)—a fascinating field of reproductive medicine—has become an increasingly utilized technique in the treatment of infertility. Continuous advancements in IVF technology have led to higher success rates in treatment. From the improvement of cell culture techniques to the development of embryo selection methods, IVF has become more efficient and safer for couples wishing to have children.

Although techniques have advanced significantly year after year, there are still risks associated with these procedures. A significant consequence of this technique is the occurrence of preterm births. Both in Romania and globally, prematurity is a significant issue among newborns, and the specific characteristics of preterm babies conceived through IVF remain a subject of research and debate.

By analyzing these characteristics, the aim is to gain a deeper understanding of the impact of technology on the future development and health of these children. Thus, this thesis will present the general context of IVF, its evolution over time, highlighting the progress and challenges encountered in the field of reproductive assistance, and subsequently, the importance and necessity of specifically addressing prematurity.

The current importance of the issue lies in the still high incidence of prematurity globally in IVF, largely due to multiple pregnancies, maternal pregnancy pathology, and the increased risk of congenital anomalies.

In vitro fertilization (IVF) has become an increasingly popular option for infertile couples in Romania, but at the same time, there must be concern about the risk of prematurity associated with this treatment. In Romania, where prematurity rates are already high, this issue is particularly relevant. Of course, the benefits of IVF treatment in treating infertility are considerable, but it is important that patients and doctors are aware of the associated risks and can make informed decisions. Improving access to quality prenatal care and closely monitoring pregnancies resulting from IVF are essential to reduce the risk of prematurity and improve perinatal outcomes in Romania.

The multidimensional concept—quality in assisted human reproduction—includes aspects related to treatment effectiveness, the impact on the health of both partners and the conceived

child, treatment costs in terms of financial expenses, and implications for family and human life.

The success of IVF is represented by the birth of a single, healthy, full-term child.

The choice of the research topic for this thesis is motivated by the increasing incidence of infertility among couples globally and the evolution of assisted reproduction technologies. Considering the complexity and challenges faced by couples undergoing IVF, the study aims to provide a comprehensive overview of the impact of this procedure in the Romanian socio-medical context.

The topic addressed enjoys increased importance in the current context, where the success rates of IVF procedures are continuously monitored and optimized. The novelty of the study lies in the detailed analysis of data obtained from one of the most prestigious mother and child health centers in Romania, Polizu Maternity Hospital, offering an updated perspective on national results and trends.

The work aligns with both international and national concerns for improving IVF practices, aligning with comparable global studies and contributing to the specialized literature with valuable data and a specific analysis for the Romanian population.

The research hypothesis assumes that optimizing the IVF protocol and personalizing care for each case can lead to an increased success rate in the conception and birth of healthy newborns, even in high-risk pregnancies, such as those resulting from IVF.

The established scientific objectives focus on identifying and analyzing the factors that influence IVF outcomes, evaluating maternal and neonatal complications, and developing recommendations for improving the IVF protocol in Romania.

The adopted research method includes the retrospective analysis of clinical data, the use of advanced statistical models to evaluate correlations and trends, as well as a multidisciplinary approach to interpret the results within a broader socio-medical context.

The research has a profoundly interdisciplinary character, combining clinical data with psychological, social, and economic aspects to create a comprehensive framework for understanding the impact of IVF on couples in Romania.

Despite the relevance and scope of the data analyzed, the research faces limitations related to the variability of clinical interventions and the retrospective nature of the study. The perspective for continuing the research suggests expanding the database to include a longitudinal series of cases and integrating standardized intervention protocols to increase the accuracy and applicability of the results.

Assisted human reproduction is one of the fastest-developing fields in medicine, advancing far beyond the imagination of those who pioneered this technique, which led to the birth of Louise Brown.

Sir Robert Geoffrey Edwards was awarded the Nobel Prize in Medicine in 2010 for the development of IVF (Figure 1).

Over 8 million children have been born worldwide with the help of IVF, and this number is continually growing . Artificial reproduction technology has come a long way, with significant advancements each year.

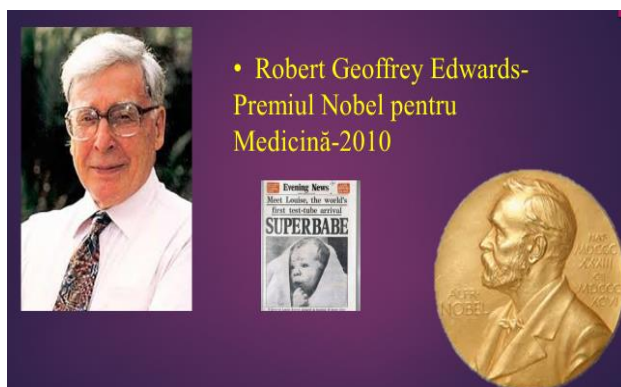


Figure 1 Sir Robert Geoffrey Edwards, Nobel Laureate.

The history of IVF in Romania is relatively recent. The first in vitro fertilization clinic in Romania was opened in Timișoara, under the coordination of Academician Prof. Dr. Ioan Munteanu, who is considered the father of IVF in Romania (Figure 2). On February 6, 1996, the first child in Romania conceived through IVF, named Daniel, was born via cesarean section. At that time, Romania became the eighteenth country in the world to successfully perform in vitro fertilization.



Figure 2 Academician Prof. Dr. Ioan Munteanu.

In Bucharest, the second state IVF clinic in Romania was established within the Prof. Dr. Panait Sârbu Clinical Hospital of Obstetrics and Gynecology, led by Academician Prof. Dr. Bogdan Marinescu. At this clinic, in 2005, the oldest woman at that time gave birth after achieving pregnancy through an IVF cycle with donated gametes (oocytes and sperm).

Currently, IVF is performed in 22 clinics across Romania (20 private and 2 state-run), with 13 of these clinics offering IVF services through the national in vitro fertilization program .

Over the past 30 years, Romania has experienced a significant population decline, primarily due to a consistent decrease in birth rates and massive emigration. While birth rates are decreasing, advancements in perinatal medicine are leading to lower perinatal mortality rates and increased survival at younger gestational ages.

Factors contributing to the declining birth rates in recent years include reduced fertility, the increasing age at which women become pregnant, greater interest in advanced education, delayed marriage, smaller family sizes, and increased use of contraceptives.

Infertility is a global health issue affecting millions of people worldwide who are of reproductive age. Data provided by the World Health Organization (WHO) indicates that 15% of couples experience difficulties in achieving pregnancy. Globally, 48 million couples face infertility, with 1 in 4 couples in developing countries being affected . The infertility rate in Romania is 1.6% for primary infertility and 15.9% for secondary infertility .

Assisted human reproduction addresses the needs of infertile couples, offering them the chance to have a child. A detailed evaluation of the infertile couple before in vitro fertilization (IVF) is essential for achieving the best outcomes and avoiding complications. This

evaluation includes assessing the quality of oocytes and male gametes, identifying subgroups of patients who require a different approach to stimulation, and evaluating factors that affect implantation as well as important lifestyle factors to maximize IVF outcomes.

Since the birth of the first IVF child, there has been rapid refinement of assisted reproduction techniques. Today, we speak of ICSI (Intracytoplasmic Sperm Injection), IMSI (Intracytoplasmic Morphologically Selected Sperm Injection), IMV (In Vitro Maturation), and AH (Assisted Hatching), all of which are complementary methods to IVF.

The steps of the in vitro fertilization procedure include:

- Evaluation and investigation of the infertile couple to identify risk factors.
- Establishing a treatment plan and providing counseling for the infertile couple.
- Controlled ovarian stimulation to obtain a sufficient number of oocytes, collected via ovarian puncture.
- Collection of gametes through ovarian puncture for oocyte retrieval (follicular aspiration); collection of sperm samples, and preparation of sperm for fertilization.
- Fertilization of oocytes—either conventional IVF or using ICSI techniques on day 0.
- Assessment of fertilization by analyzing the morphology of oocytes and scoring fertilization on day 1.
- In vitro culture of embryos on days 2, 3, 4, 5, and 6. Evaluation and selection of embryos for embryo transfer. Cryopreservation/vitrification of surplus embryos [44].
- Embryo transfer.

Performance in assisted human reproduction is measured by maximizing the chances of successful pregnancy, minimizing the occurrence of multiple pregnancies, and reducing the risk of complications. For quality control and assurance, indicators are classified into three categories: performance indicators, operational and process entry indicators.

As with any medical or surgical treatment, IVF involves a series of risks and complications, some related to the procedure itself and others related to birth outcomes . These potential complications present a significant and constant challenge for doctors who care for patients both during and after the IVF process. Risks are present at each stage of the process, from the

medication phase (ovarian hyperstimulation syndrome, adverse drug effects) to the oocyte retrieval phase (hemorrhage, infection), pregnancy phase (multiple pregnancy, velamentous cord insertion, ectopic/heterotopic pregnancy), and even up to the increased risk of premature birth and congenital anomalies in newborns.

The European Society of Human Reproduction and Embryology (ESHRE) recommends that embryo selection for transfer should primarily be based on the stage of development and morphological aspects. ESHRE advises transferring a single embryo to avoid multiple pregnancies. The decision regarding the number of embryos to be transferred should be based on the quality of the embryos, the stage of development, the woman's age, ovarian response, and the rank of the procedure. No more than two embryos should be transferred, and the remaining embryos should be cryopreserved, donated, or discarded, with the decision regarding the use of the remaining embryos being made based on the patient's wishes and national legislation.

Complications in patients with multiple pregnancies include an increased risk of gestational diabetes, hypertensive disorders (pregnancy-induced hypertension, chronic hypertension, preeclampsia, HELLP syndrome, hepatic steatosis), cesarean delivery, anemia, premature rupture of membranes, preterm contractions and labor, preterm birth, placental abruption, and postpartum hemorrhage. The risk of developing hypertension, preeclampsia, and eclampsia is three times higher in twin pregnancies and nine times higher in triplet pregnancies. Maternal mortality associated with multiple births is 2.5 times higher than in singleton births .

Fetal complications to note include an increased risk of anatomical and genetic anomalies, growth disorders, prematurity with all associated complications, and issues related to monochorionicity (twin-to-twin transfusion syndrome). The transfer of a single embryo, with cryopreservation of the remaining embryos, should be the ideal strategy .

The objective of IVF treatments is to achieve a singleton pregnancy. The goal is to maximize the probability of pregnancy while minimizing the risk of multiple pregnancies, with the only effective way being the transfer of a single embryo.

From the moment of an infertility diagnosis, there is a psychological impact at both the individual and couple levels. Psychological support and counseling during assisted reproduction treatments are strongly recommended by researchers and clinicians . In recent years, numerous studies have been conducted on the psychosocial levels and the impact on

the lives of couples undergoing assisted human reproduction techniques. Antepartum, infertile women undergoing repeated IVF treatments have a higher risk of depression and stress, due to the arduous process they undergo to achieve pregnancy through IVF (long-term treatments, numerous medical visits, high costs, various traumatic procedures, and uncertain results).

Between 1% and 6% of children in industrialized countries are born through assisted reproduction techniques such as IVF/ICSI, which are associated with a higher rate of cesarean births compared to naturally conceived children . The rate of elective cesarean sections is higher in IVF pregnancies than the rate of emergency cesarean sections, compared to cesareans in naturally conceived pregnancies. This trend is also evident in IVF/ICSI with either frozen or fresh embryos, compared to naturally conceived pregnancies .

The increased rate of cesarean sections in IVF is primarily due to the higher incidence of multiple pregnancies, which most often result in cesarean delivery. Women who undergo in vitro fertilization are usually older (over 35 years), with a higher risk of developing conditions that lead to a cesarean section indication . In naturally conceived pregnancies, there are other antenatal complications that lead to a higher incidence of cesarean section indications compared to IVF pregnancies (see Table 5.2) .

In 1985, the first Australian data were published showing a higher rate of preterm births following IVF. Preterm birth, low birth weight, perinatal mortality, and admission to intensive care are more frequent with IVF. The prevalence of prematurity in in vitro fertilization increases exponentially due to the high incidence of multiple pregnancies, but it was later observed that this also occurs in single pregnancies. IVF techniques increase the incidence of both late preterm and extremely preterm births.

Major congenital anomalies represent the third leading cause of neonatal death, with an estimated 295,000 newborns dying within the first 28 days of birth each year worldwide due to congenital anomalies. The association between assisted reproductive technology (ART) and the risk of congenital malformations was first reported in the 1980s when Lancaster found a higher incidence of neural tube defects and cardiovascular defects in children born through IVF. Congenital defects and preterm birth are common and complex conditions contributing to perinatal/neonatal mortality and morbidity worldwide. In particular, IVF children represent a major clinical and epidemiological issue, considering that 1 to 2% of children born annually are conceived through in vitro fertilization.

Assessing the risk for congenital malformations is a fundamental step for appropriate preconception counseling.

Original Part

Working Hypothesis and Objectives

Careful monitoring of pregnancy should lead to completion as close to term as possible, without major complications that could affect the quality of life of those involved—both children and parents—despite the internationally recognized risks associated with IVF.

The study is conducted in a Level III maternity hospital, where high-risk pregnancies from across the country, particularly from the southern region, are monitored. Given the increasing number of these newborns, I aim to outline their perinatal characteristics.

This research aims not only to complement existing knowledge but also to provide new perspectives and deepen the understanding of this crucial topic in the field of assisted human reproduction, highlighting both the positive outcomes and the ongoing concerns and uncertainties.

The general objective is to evaluate and improve perinatal care for preterm infants conceived through in vitro fertilization, thereby enhancing perinatal outcomes.

The specific objectives are:

- To identify the clinical and care-related characteristics of preterm infants resulting from IVF procedures compared to those conceived naturally;
- To analyze the morbidity and mortality rates of IVF preterm infants and identify the specific associated risk factors;
- To evaluate the impact of in vitro fertilization techniques and technologies on the perinatal status of preterm infants;
- To explore optimized perinatal care strategies tailored to the specific needs of IVF preterm infants;
- To contribute to the development of evidence-based clinical guidelines for the management of preterm infants conceived through IVF.

General Research Methodology

Statistical Analysis Methods

After entering the data obtained from the study protocols into the database fields, they were processed using SPSS version 23.0 and Excel software packages.

For descriptive statistics, the mean and standard deviation were calculated, as well as medians and quartiles for quantitative variables (Study II), while frequencies and percentages were calculated for qualitative variables (Study I and II). In comparing quantitative data, depending on the normality of the data, the Student's t-test (for two groups with normally distributed data) and the Mann-Whitney test (for data not normally distributed) were used. Quantitative data were tested for normality and homogeneity of variances using Levene's test.

For categorical data (summarized as frequencies and percentages), Fisher's exact test (binary data) and Pearson Chi-square test, as well as the Likelihood Ratio test (if 20% of the expected frequencies were less than 5), were used.

When more than two groups were compared and the general significance test indicated significance, multiple comparison tests (post hoc) were applied to determine between which groups there was statistical significance.

In Study II, because the sample was divided based on prematurity and gestational age categories, the tests applied to subgroups were Bonferroni corrected.

A probability of error less than 5% ($p < 0.05$) was considered the threshold for significance.

Study I. Impact of In Vitro Fertilization on Neonatal Outcomes

Context of In Vitro Fertilization

In recent decades, assisted reproduction technologies, particularly in vitro fertilization (IVF), have become a significant solution for couples facing infertility. Despite significant advances in the field, pregnancies resulting from IVF are often associated with a range of challenges and risks, including increased incidence of prematurity and perinatal complications.

Importance of the Study in the Romanian Context

Romania, with an expanding network of IVF clinics and a rising number of couples using this method, faces the need for a deeper understanding of the impact of IVF on neonatal

outcomes. Our study aims to contribute to this understanding by providing insights based on real data collected at Polizu Maternity, a reference center for high-risk pregnancies.

Study Objectives

Through a retrospective analysis of newborns resulting from IVF procedures, the study aims to evaluate the rate of prematurity and its complications, compare various characteristics of IVF newborns with those conceived naturally, and pay special attention to the impact of multiple pregnancies on neonatal outcomes and the prevalence of cesarean sections in IVF pregnancies.

Material and Method

Selection and Characterization of the Study Population

Our study was designed as a retrospective population analysis focused on newborns resulting from IVF pregnancies. The study population included 326 newborns conceived through IVF between 2011 and 2016.

Study Context

The research was conducted at Polizu Maternity, a Level III maternity known for its care of high-risk pregnancies in the southeastern region of Romania. Although this maternity does not perform IVF procedures, it provides comprehensive support for pregnancies resulting from such procedures, offering an appropriate setting for the study.

Data Collection and Analysis

We analyzed the increasing rate of newborns obtained through IVF, noting an upward trend from 1.28% in 2011 to 2.6% in 2016. Demographic data, including the type of pregnancy and mode of delivery, as well as Apgar scores and the need for resuscitation at birth, were collected and compared between full-term and preterm newborns. We examined gender distribution and identified trends related to prematurity.

Statistical Methodology

To assess the statistical significance of differences between groups and the association of various clinical conditions with IVF birth outcomes, Pearson Chi-Square test was used.

Variables such as the type of pregnancy, mode of delivery, Apgar score, and others were analyzed to determine their impact on neonatal outcomes.

Results and Discussion

With a relatively recent history in Romania, in vitro fertilization has offered infertile couples the chance to have children. Although there are 22 accredited clinics, 12 of which were selected for the National IVF Program, some couples choose to undergo IVF in countries like Hungary, Greece, Israel, Ukraine, Belgium, Lithuania, and the Czech Republic (Figure 8.1).

Polizu Maternity—where the study was conducted—is a Level III maternity that does not perform IVF procedures but provides care for high-risk pregnancies in southeastern Romania (Figure 8.2).

The study includes a cohort of 326 newborns conceived through IVF between 2011 and 2016.

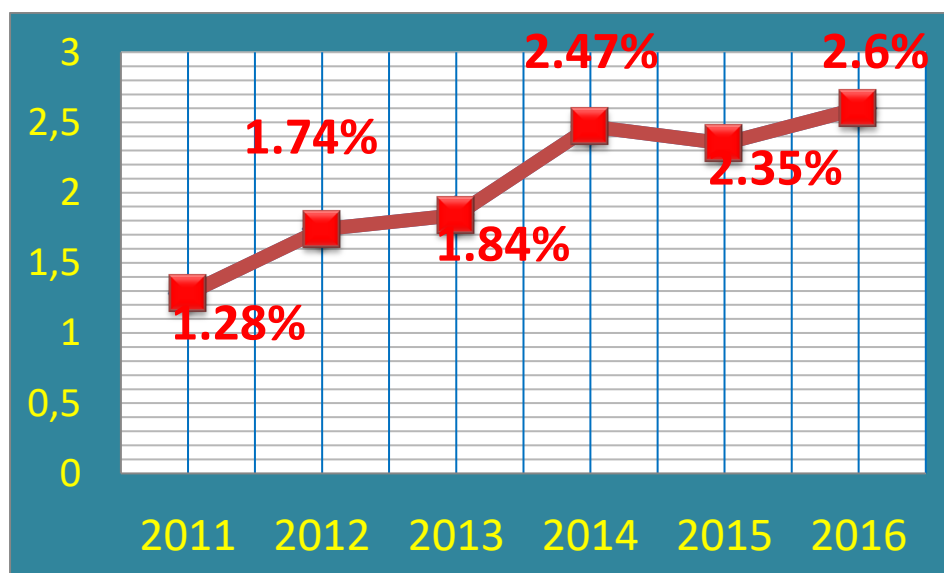


Figure no 3- Incidence of IVF infants between 2011-2016

The rate of prematurity during the study period was 59.2%, a much higher incidence than reported in international data. A study involving 179,960 newborns from IVF pregnancies indicates a prematurity rate of 28.4% for both singleton and multiple IVF pregnancies .

The rate of premature newborns from singleton IVF pregnancies was 8.8%, slightly higher than a recent international study involving 23,111 pregnancies, where the rate was 7.13% .

Premature newborns from IVF twin pregnancies are significantly more frequent compared to full-term newborns. These findings highlight a strong association between assisted reproductive technologies and preterm birth, emphasizing the importance of careful monitoring and appropriate management of multiple IVF pregnancies.

The percentage of twins among the total number of IVF newborns is 60.4%, a much higher rate than that found in the literature. This result is due to the transfer of two or more embryos. Although ESHRE (the European Society of Human Reproduction and Embryology) has introduced a strategy to minimize multiple births by recommending the transfer of a single embryo, Romania lacks legislation on this issue, and clinics continue to transfer two or more embryos. The decision on the number of embryos to be transferred is made by the fertility clinics, with the patient's consent, and should be based on embryo quality, development stage, patient age, and the procedure's rank.

Literature data show that 43% of children conceived through assisted reproductive techniques are from multiple pregnancies .

Birth weight is an important risk factor for premature infants, with 46.4% weighing between 1500-2500 grams, 24% weighing between 1000-1499 grams, and 13.5% weighing less than 1000 grams.

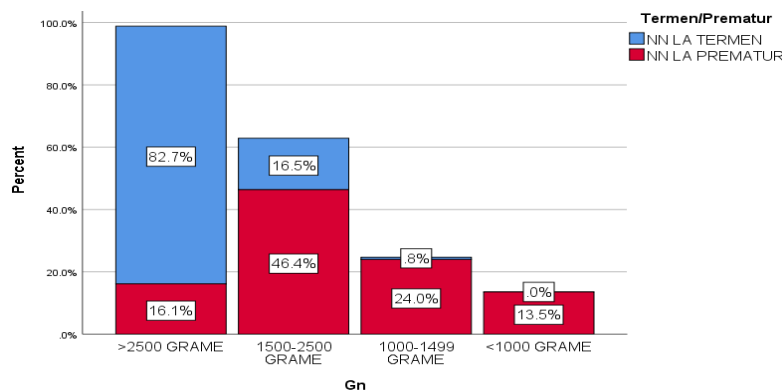


Figure no 4 Incidence of term and preterm IVF newborns related to birth weight

IVF premature infants have a higher incidence of intrauterine growth restriction compared to full-term newborns, with rates of 7.3% versus 3.8%.

Cesarean delivery was the predominant mode of birth for both singleton and multiple pregnancies. The rate of elective cesarean sections is higher in IVF cases compared to emergency cesarean sections. The cesarean section rate in the current study is significantly

higher than reported in international studies, which range from 21.2% to 47.2% . This elevated rate is largely due to the increased risk of cesarean delivery in multiple pregnancies, but it also appears related to greater anxiety from both parents and doctors, who prefer to avoid complications from natural birth that could affect the health of a long-awaited child.

Regarding neonatal resuscitation for IVF preterm infants, it was statistically significantly more common compared to full-term newborns. Extreme preterm infants required resuscitation at birth in 82.6% of cases.

97.7% of full-term newborns and 91.3% of late preterm IVF infants had Apgar scores above 8 and did not require resuscitation at birth. Low birth weight was also a risk factor for invasive resuscitation, with 72.4% of newborns weighing less than 1000 grams needing resuscitation measures.

Maternal infections were significantly associated with the need for neonatal resuscitation. The need for resuscitation was associated with multiple pregnancies, younger gestational age, low birth weight, and the presence of maternal infections. Cesarean section and maternal age over 40 did not constitute risk factors for the need for resuscitation.

Respiratory distress syndrome (RDS) was diagnosed in 87 IVF preterm infants, representing 45% of all IVF preterm infants. Among extreme preterm infants (gestational age <28 weeks), RDS was present in 100% of cases, a higher percentage compared to the literature for this gestational age in naturally conceived children (85%). For late preterm infants, the percentage of those with RDS is also higher than the literature for naturally conceived children (13% vs. 6.3%).

Early-onset sepsis (EUN) was present in 9.7% of all IVF newborns and 16.1% of all IVF preterm infants. Among extreme preterm infants, 39.1% developed EUN, a rate 3.5 times higher than that of preterm infants from natural pregnancies for the same gestational age category (11.1%) . EUN was significantly associated with maternal smoking and infection, with *E. coli* being the most frequently involved pathogen. Perinatal asphyxia, low birth weight (<1500 grams), and intrauterine growth restriction were significant risk factors for EUN.

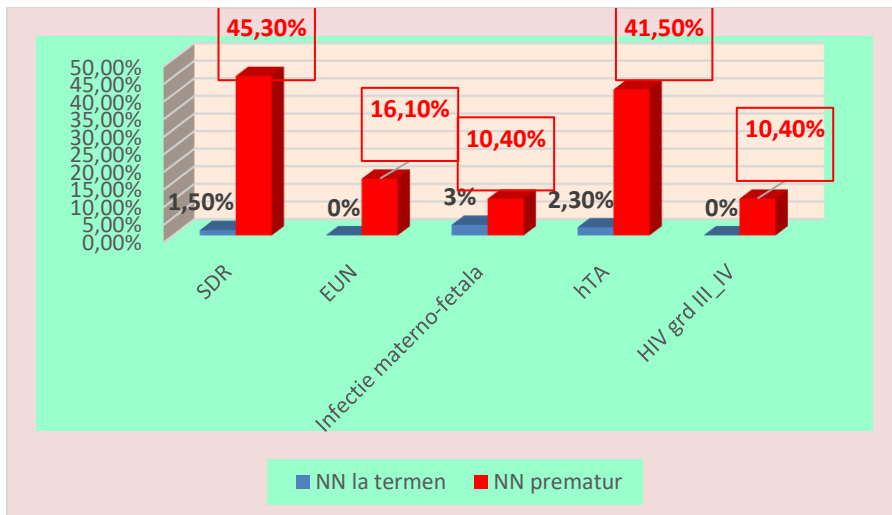


Figure no 5 Morbidity of preterm IVF infants

Cerebral hemorrhage grade III-IV was detected in 4.2% of all IVF newborns, 7.2% of all preterm infants, and 60.9% of extreme preterm IVF infants. This is 3.1 times higher than the rate reported in international studies for naturally conceived newborns with a gestational age <28 weeks.

This major complication was significantly associated with maternal infections, younger gestational age, severe asphyxia, multiple pregnancies, and low birth weight.

The majority of extreme preterm infants came from mothers younger than 35 years (78.3%), while 8.7% were from mothers over 40 years old.

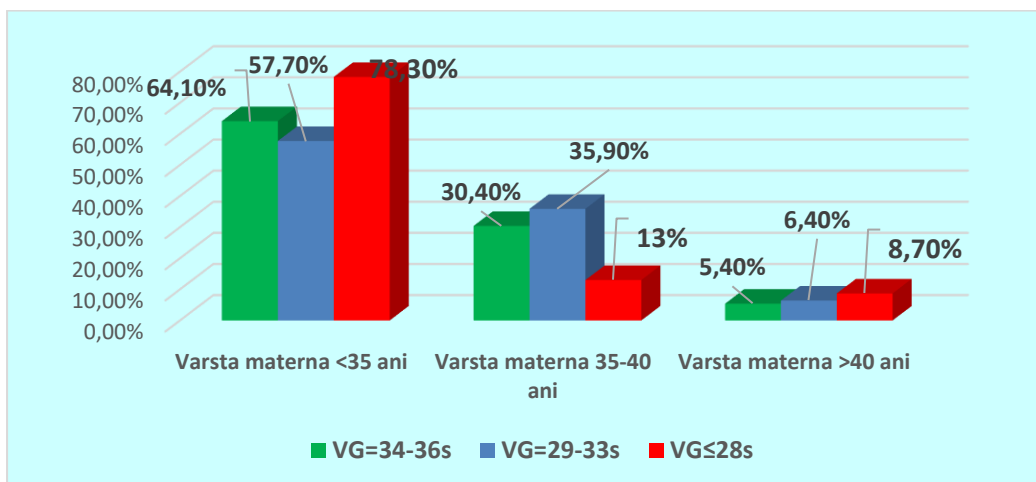


Figure no 6 The rate of IVF newborns related to maternal age categories

A significant percentage of extreme preterm infants were born to women with genital infections (69.6%), which is approximately twice as high as for late preterm infants (33.1%) or full-term newborns (34.8%).

Intrauterine growth restriction had the highest incidence among extreme preterm infants (21.7%), increasing the risk of neonatal morbidity and mortality.

Congenital malformations were detected in 14.6% of all IVF newborns.

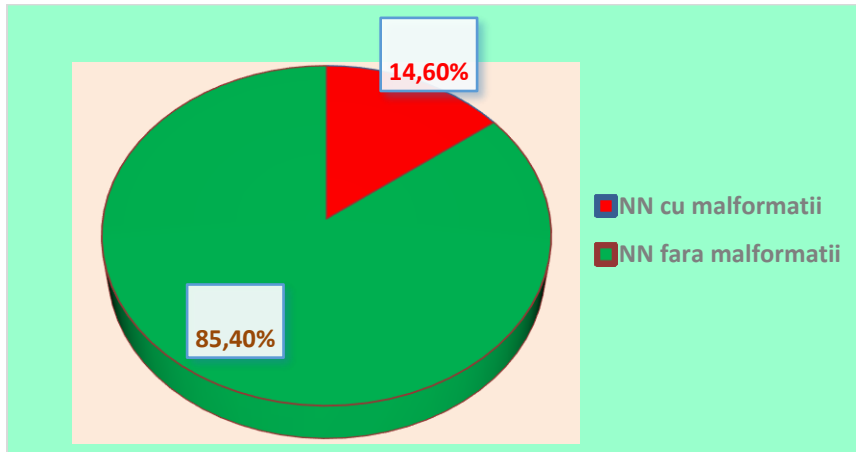


Figure no 7 The prevalence of congenital anomalies

By gestational age categories, congenital malformations were significantly more common among extreme preterm infants. Specifically, 43.5% of extreme preterm infants had malformations, compared to 22.1% of those with a gestational age of 29-33 weeks. This is in contrast to late preterm infants (6.5%) and full-term IVF newborns (11.3%).

The prevalence of congenital malformations was statistically significantly higher in male newborns compared to females, consistent with international studies on naturally conceived infants.

Cardiac malformations were the most common, being statistically significantly more frequent in extreme preterm infants and those with a gestational age of 29-33 weeks, compared to late preterm infants and full-term newborns. However, no complex cardiac malformations were observed.

The duration of neonatal intensive care unit (NICU) stay and total hospital stay were inversely proportional to gestational age and birth weight.

1.5% of full-term newborns and 4.3% of late preterm infants required hospitalization for more than 30 days. All surviving extreme preterm infants required prolonged hospitalization, lasting more than 90 days.

The mortality rate for preterm infants was 3.3% of the total number of IVF newborns and 5.6% of the total number of IVF preterm infants.

The survival rate at discharge was 65.2% for extreme preterm infants, 96.2% for those born at 29-33 weeks, and 100% for those born at 34-36 weeks.

Particularities of Premature Infants from IVF Twin Pregnancies Compared to Spontaneous Twin Pregnancies

Recently, there has been a notable increase in the number of twin pregnancies. The goal of IVF treatments is to achieve a singleton pregnancy. Twin pregnancies are considered high-risk for both the mother and the fetuses/newborns. Multiple pregnancies are an iatrogenic complication of in vitro fertilization (IVF). Internationally, there is an effort to reduce the incidence of twin pregnancies due to associated risks. Well-organized medical care for IVF twin pregnancies aims to achieve delivery as close to term as possible, with lower morbidity and mortality compared to naturally conceived twins.

Materials and Methods

Comparative and statistical analysis focused on the following aspects: maternal pathology, mode of delivery, gestational age of the newborns, adaptation to extrauterine life, admission to neonatal intensive care, short-term and long-term complications, hospitalization duration, and neonatal mortality among twins from both IVF and spontaneous pregnancies. Data were obtained from clinical observation sheets of mothers and newborns.

The study included two groups over a period of two years, 2018-2019:

- Group I: Newborns from multiple pregnancies achieved through IVF.
- Group II: Newborns from spontaneously conceived multiple pregnancies (non-IVF group).

Results and Discussion

During the study period, 2018-2019, the rate of newborns from multiple pregnancies was 4.8% (314 newborns) of the total number of newborns (6476). Among these, 86 newborns were from IVF pregnancies and 228 newborns were from spontaneous pregnancies.



Figure no 8 .IVF twins

In the studied period, twins conceived through IVF represented 1.3% of the total number of newborns, whereas spontaneously conceived twins (non-IVF) accounted for 3.5%. Globally, the rate of spontaneous multiple pregnancies is under 2% .

Twin pregnancies are considered one of the greatest risks associated with IVF. The likelihood of a multiple pregnancy is 20 times higher following reproductive treatments.

At Maternity Polizu during the study period, the incidence of newborns from multiple pregnancies was 4.8% of the total number of newborns. Approximately 30% of twin pregnancies resulted from IVF techniques, which is consistent with figures reported in the literature.

IVF twins accounted for 1.3% of the total number of newborns, 27.2% of the total number of newborns from multiple pregnancies, and 50.3% of the total number of IVF newborns.

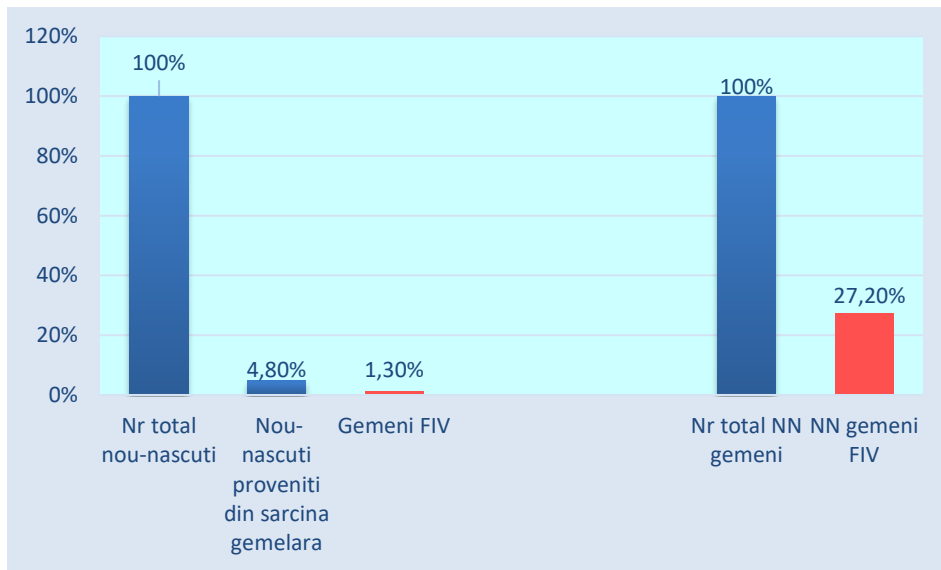
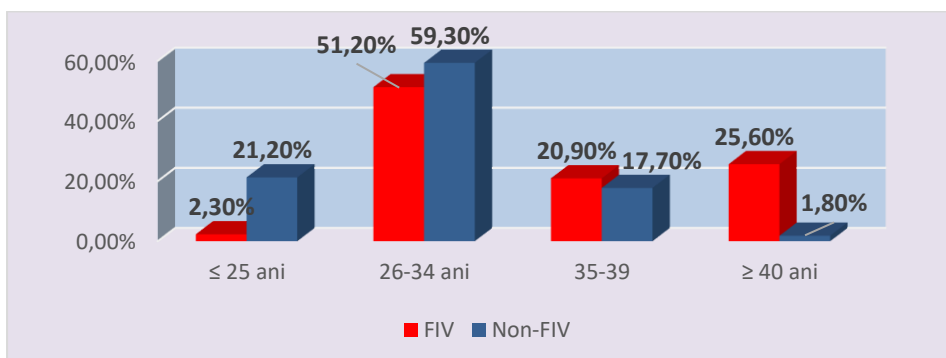


Figure no 9 The prevalence of IVF and non-IVF twins

A notably higher rate of spontaneously conceived twins was observed, at 3.5% of the total number of newborns, whereas the global incidence of spontaneous twin pregnancies is under 2%.

The study focused on a comparative analysis between IVF twins and non-IVF twins.

Maternal age was higher in the IVF group. The average maternal age was 34 years in the IVF group and 31 years in the non-IVF group, with a statistically significant difference (p-value 0.000008 - Mann-Whitney U). Additionally, 25% of IVF twins were born to mothers over 40 years old, compared to 1.8% of spontaneously conceived twins (p-value 0.000003 - Pearson Chi-Square). In contrast, natural twin pregnancies are also observed in mothers under 25 years of age, including minors.



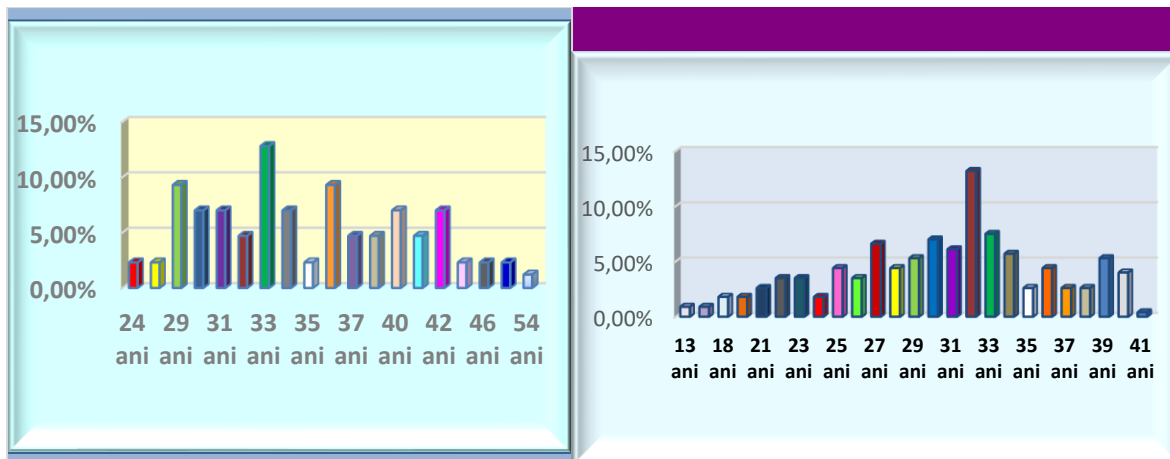


Figure no 11 The prevalence of IVF and non-IVF twins related to maternal age

Twin pregnancies achieved through IVF are monitored much more closely than spontaneously conceived twins, with a statistically significant difference (p-value 0.005891 - Likelihood Ratio).

Maternal pathology in IVF twin pregnancies is statistically significantly more frequent than in spontaneous twin pregnancies (p-value 0.000692 - Pearson Chi-Square). Conditions such as hypertension, hypothyroidism, and thrombophilia are encountered more frequently in IVF patients compared to those with spontaneous conceptions (p-values 0.000041, 0.027270, and 0.000000 respectively). The risk of developing hypertension, preeclampsia, and eclampsia is three times higher in twin pregnancies. In this study, the incidence of hypertensive disorders was eight times higher in mothers of IVF twins. Recent meta-analyses indicate that IVF pregnancies have a higher incidence of hypertensive pathology, regardless of plurality .

Contrary to literature suggesting that placental pathology is more frequent in IVF pregnancies, it was more common in spontaneously conceived pregnancies in this study. Maternal infections had a similar incidence in both groups, with Group B Streptococcus (GBS) and E. coli being the most frequently encountered pathogens.

The rate of prematurity in IVF twin pregnancies (67.9%) was lower compared to spontaneous pregnancies (78%), likely due to the careful monitoring associated with IVF pregnancies. However, the rate of prematurity in both groups is higher than reported in international studies (60%) .

Late preterm IVF infants represented the largest category in both groups, with a lower proportion in the IVF group compared to the non-IVF group (35.7% vs. 49.8%). International

studies indicate that IVF twins are born on average at 35.3 weeks , while in our study, IVF twins were born on average at 34.2 weeks.

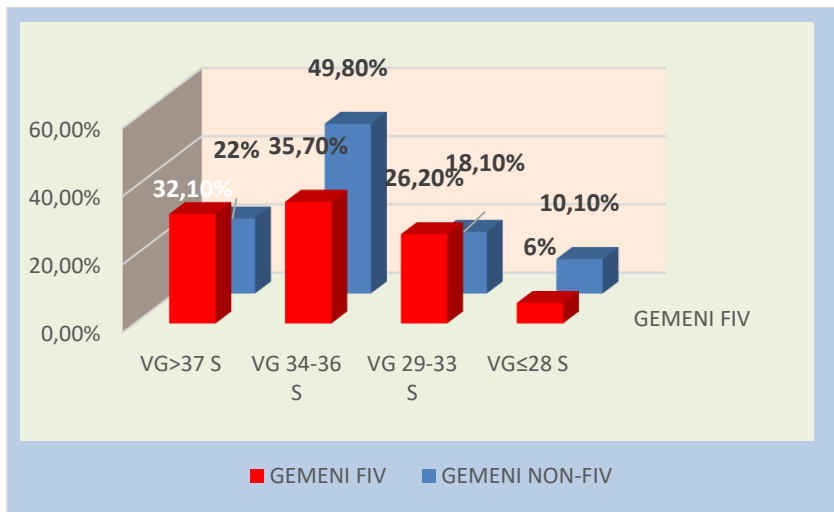


Figure no 12 The rate of IVF and non-IVF twins related to gestational age

Monitoring of IVF pregnancies leads to a lower rate of extreme prematurity, with IVF twins born before 28 weeks being less common than naturally conceived twins (6% vs. 10.10%), though this difference is not statistically significant.

International studies report that the average birth weight of twins is 2347 grams. In our study, the average birth weight for IVF twins was 2220 grams, while those from spontaneous twin pregnancies averaged 2225 grams .

IVF twins were delivered via cesarean section in 95.2% of cases, compared to 69.9% for spontaneously conceived twins. International studies show that IVF multiple pregnancies, particularly those at 34-36 weeks, have a higher risk of cesarean delivery compared to natural pregnancies. For instance, an Australian study found a cesarean rate of 45.8% in multiple pregnancies .

IVF twins also had a higher rate of congenital heart defects (6%) compared to naturally conceived twins (2.3%).

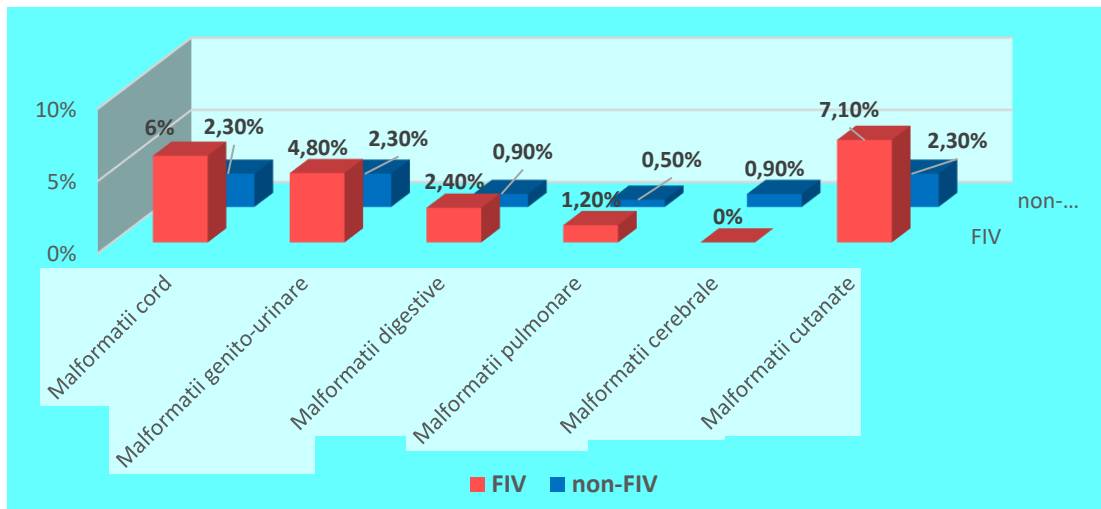


Figure no 13 The prevalence of congenital malformation in IVF and non-IVF twins

Congenital cardiac malformations in IVF-conceived twins included atrial septal defects, ventricular septal defects, pulmonary stenosis, and one case of hypoplastic left heart. In spontaneously conceived twins, ventricular septal defect was predominant, but other malformations such as atrial septal defect, aortic arch hypoplasia, and isthmus aorta were also observed.

IVF twins had a higher incidence of genitourinary and digestive malformations compared to spontaneously conceived twins. Central nervous system malformations were absent in IVF twins but identified in spontaneously conceived twins. Additionally, a higher percentage of IVF twins required surgical interventions for congenital malformations.

Preimplantation Genetic Diagnosis (PGD) was performed in a very small number of cases due to high costs and lack of coverage by IVF programs. Embryo reduction was carried out in cases of Down syndrome and triplet pregnancies to increase the chances of survival for two of the twins.

IVF twin pregnancies present an increased risk due to risks associated with both spontaneous twin pregnancies and advanced maternal age and maternal pathology, particularly hypertension. However, careful monitoring of IVF pregnancies contributes to a lower rate of maternal and neonatal morbidity and mortality compared to spontaneous twin pregnancies. Although the incidence of prematurity is lower in IVF twin pregnancies compared to spontaneous ones, the percentage remains higher than reported in the literature.

Conclusions and Personal Contributions

Conclusions

Achievement of Research Objectives

In this doctoral thesis, my goal was to investigate the impact of in vitro fertilization (IVF) on the incidence of prematurity and to identify risk factors and complications in IVF newborns. The established objectives specifically aimed at a detailed understanding of the demographic and clinical characteristics of IVF newborns and comparing them with naturally conceived newborns, to assess the specific impact of IVF on neonatal health.

The results presented demonstrate that the research objectives were largely achieved. The demographic analysis of IVF newborns, focusing on annual trends and comparing the rate of prematurity, highlighted a gradual increase in the number of IVF newborns as well as a higher rate of prematurity compared to naturally conceived newborns. These findings confirm the initial hypothesis and emphasize the need for improved prenatal care protocols for mothers undergoing IVF.

IVF pregnancies are characterized by a higher risk due to maternal pathology and the prevalence of multiple pregnancies. This study confirmed that the incidence of prematurity is significantly higher among IVF newborns, a phenomenon largely attributed to multiple pregnancies. A strong correlation was observed between multiple pregnancies and increased risks of complications for both mother and fetus.

Additionally, cesarean section was found to be the predominant method for delivery in IVF pregnancies, regardless of the number of fetuses. This trend underscores the need for careful monitoring and meticulous birth planning in IVF pregnancies to optimize success rates and minimize associated risks.

Our results also highlight the importance of adaptation to extrauterine life, particularly for premature newborns who require admission to neonatal intensive care units. Short- and long-term morbidity remains a major concern, with a particular focus on congenital malformations at early gestational ages. Cardiac and cerebral malformations were identified in a significant percentage of cases, emphasizing the need for appropriate psychological counseling both during and after hospitalization to support affected families.

The increasing age at which women choose to conceive via IVF represents another risk factor requiring attention, involving potential complications for both mother and fetus. Despite these challenges, the survival rate of IVF newborns reflects medical advancements in assisted reproduction and neonatal care.

Therefore, the conclusions of this study highlight the complexity and challenges associated with IVF pregnancies, emphasizing the importance of careful monitoring, specialized interventions, and continuous support for families choosing this path to conception. These findings contribute to the existing knowledge base and should guide clinical practices and public health policies to improve outcomes for IVF pregnancies. The analysis also revealed several neonatal complications associated with IVF, including respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC). These findings underline the importance of careful monitoring and early interventions to minimize risks for IVF newborns.

In conclusion, the research achieved the established objectives by identifying and analyzing the specific characteristics of IVF newborns, providing a foundation for improving clinical practices and public health policies related to perinatal care for IVF mothers. By significantly contributing to the understanding of IVF's impact on neonatal health, my thesis aims to facilitate the development of effective strategies for the care and support of this vulnerable group of newborns and their families.

Advantages and Disadvantages Identified

Advantages

In Romania, in vitro fertilization (IVF) offers significant advantages, including notable advancements in reproductive technologies that provide infertile couples with a chance at parenthood that they would otherwise not have. Data analysis from Section 4.3 highlighted the increasing accessibility of these procedures, supported by government initiatives that cover part of the treatment costs. A remarkable aspect of IVF in Romania is the adaptability of clinics to the latest protocols and assisted reproductive techniques, which enhance pregnancy success rates and reduce complication rates.

However, IVF is associated with considerable disadvantages. The substantial costs of IVF can be prohibitive for some of the population, given that multiple treatments are often required to achieve a successful pregnancy. Another challenge is related to psychological and emotional

aspects, with couples undergoing IVF procedures experiencing significant stress and requiring adequate psychological support.

Comparing different gestational age categories, the data indicate an increased incidence of complications and the need for special care for IVF newborns, especially in cases of multiple pregnancies. This underscores the importance of risk management strategies and careful monitoring protocols for IVF pregnancies to minimize risks for both mother and child.

IVF in Romania provides significant advantages for infertile couples but comes with technical, economic, and health challenges that require continuous attention from healthcare providers and policymakers. Efforts should continue to improve accessibility, efficacy, and psychological support associated with IVF procedures while maintaining high standards of safety and care quality for all patients.

Originality of the Work

The originality of this thesis lies in its innovative and comprehensive approach to the impact of in vitro fertilization (IVF) on pregnancies and newborns. A unique perspective is offered by the fact that the analysis was conducted by a neonatologist who had no access to information about the pregnancy progression until birth, highlighting the impact of immediate perinatal conditions on neonatal health.

Distinctively, the study evaluates how maternal pathology and lifestyle have influenced newborn adaptation to extrauterine life, providing a new level of understanding of the complexity and diversity of neonatal experiences in the context of IVF. Another original aspect identified is the increased rate of cesarean sections, often justified by abnormal presentation of twins and membrane rupture, offering a critical perspective on obstetric practices in multiple IVF pregnancies.

Significantly, while newborns were affected by conditions such as perinatal asphyxia, respiratory distress syndrome (RDS), hypotension, and anemia, neurological outcomes were surprisingly favorable, with cerebral hemorrhage not exceeding Grade II in the 2018-2019 study period. This highlights the resilience and recovery potential of premature infants, even in the face of significant initial challenges.

The thesis also stands out for identifying an increased incidence of congenital malformations, particularly cardiac malformations. However, complex forms of these malformations were

rare, contributing to the existing literature by elucidating the specific profile of malformations associated with IVF.

Overall, through a multidimensional approach and focus on often-overlooked elements in the literature, the thesis claims a distinct position in neonatal research, highlighting key aspects that influence clinical evolution and neonatal outcomes in the context of IVF. This perspective not only adds to the existing body of knowledge but also provides a basis for guiding future research and improving clinical practices.

Unresolved Issues and Future Research Directions

Although my study provided a comprehensive analysis of preterm births resulting from in vitro fertilization (IVF) and identified significant factors associated with their health, it also highlighted certain limitations and unresolved issues. These aspects pave the way for new research opportunities and deeper exploration of the topic.

One primary unresolved issue is the long-term impact of IVF on the health of children. The current study focused on immediate effects and perinatal complications, leaving aside aspects related to the later development of children born through IVF. Longitudinal studies are needed to track the development of these children over several years.

Another identified issue relates to genetic diversity and epigenetic factors involved in IVF. The current study could not delve deeply into how genetic manipulation and in vitro culture conditions might influence gene expression and embryo development. This represents a broad research area requiring multidisciplinary approaches and advanced techniques in genetic and epigenetic analysis.

Additionally, the research underscored significant differences between IVF clinics in Romania and the need for standardization of practices and procedures. An important future research direction would be the evaluation and improvement of clinical protocols to ensure uniform quality of IVF services nationwide.

Moreover, the study highlighted the need for a more detailed exploration of the psychological and emotional support required by couples opting for IVF as a conception method. Investigating the emotional and psychological impact and developing dedicated support programs could enhance the IVF experience and outcomes.

In conclusion, the research has raised new questions and emphasized the need for a multidisciplinary and integrated approach to fully understand the impact of IVF on the health of children and their families. Future studies should explore these directions, contributing to the improvement of assisted reproductive technologies and optimizing care for couples undergoing IVF.

Personal Contributions

In the case studies analyzed, I made significant contributions by identifying annual trends among newborns conceived through in vitro fertilization (IVF) and conducting a comparative analysis between different gestational age categories. These case studies were essential for a deep understanding of the impact of IVF on prematurity and associated risks.

By collecting and analyzing data from multiple IVF clinics in Romania, I was able to identify annual trends, observing a progressive increase in the rate of IVF newborns. This trend reflects both the growing accessibility of assisted reproductive technologies and socio-cultural changes.

Using complex data collected from our study, I performed a detailed comparative analysis between IVF newborns classified by gestational age. I specifically examined prematurity rates, associated complications, and the need for post-natal interventions, highlighting increased risks for lower gestational age categories. This analysis provided new insights into clinical management and the specific needs of IVF newborns, contributing to the development of recommendations for medical practice and care protocol improvements.

In the detailed research section of my thesis, I substantially contributed to identifying risk factors and complications associated with IVF newborns, with a particular focus on the need for resuscitation at birth, respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), and other relevant complications. These findings are crucial for improving clinical practices and ensuring the best possible care for these newborns and their mothers.

Analyzing the collected data, I identified that prematurity, low birth weight, and multiple pregnancies are significant risk factors for the need for resuscitation at birth among IVF newborns. My contribution included using advanced statistical models to assess the risk associated with each of these factors, thus providing a solid foundation for improving birth protocols and preparing medical teams.

In addition to the mentioned complications, the research also explored the relationships between IVF and other newborn health issues, including congenital malformations and retinopathy of prematurity. Based on the analysis conducted in my study on the impact of IVF on newborns and associated complications, I propose the following measures to improve clinical practices in the field of IVF, aiming to reduce risks for both newborns and mothers.

I propose implementing a standard set of procedures and practices across all IVF clinics in Romania. This would include detailed protocols for the handling of oocytes and embryos, as well as in vitro culture conditions, to ensure the highest chances of IVF success and to minimize the risks of postnatal complications.

IVF pregnancies should be monitored more closely, with regular assessments to identify early signs of complications, such as increased risk of prematurity or the development of respiratory distress syndrome (RDS). This could involve more frequent ultrasound screenings and monitoring of the mother's and fetus's health.

Based on identified risk factors for the need for resuscitation at birth and associated complications, I recommend developing personalized birth plans for mothers who conceived through IVF. This could include planning the mode of delivery and preparing neonatology teams for rapid interventions if necessary.

I propose the development of educational and support programs for couples opting for IVF, to inform them about potential risks and how to mitigate them. This could include counseling on maintaining a healthy lifestyle during pregnancy and the importance of regular health monitoring.

I encourage continued research in the field of IVF, with a special focus on identifying risk factors for complications and developing new techniques and treatments to enhance the safety and efficacy of IVF. This could involve studies on the epigenetic impact of IVF and genetic manipulations.

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