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Stela CIOBANU (CASAP)

Maternal-fetal complications in pandemic infection with SARS-CoV-2 virus

SUMMARY

Scientific leader

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Mr. (Mrs.).....

COMPOSITION

Doctoral Commission

Named by order of the Rector of the Transilvania University of Brasov

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Any assessments or observations on the content of the work will be transmitted electronically in due time, to the address of the casapstela@yahoo.com

At the same time, we invite you to take part in the public meeting for the defense of the doctoral thesis.

Thank you.

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Preface

COVID-19 has created huge challenges in the world's medical system. All health systems are vulnerable and there are practical steps that all countries can take, not only to increase the available resources, but also to ensure the ability to adapt and use these resources differently, in the most varied scenarios.

The ability of the healthcare system to transform and evolve is essential in meeting long-term structural challenges. It draws on the core functions of the health system: governance, financing, resource generation and service delivery, and organizes its findings around a set of strategies that policymakers can use to strengthen the resilience of their health systems.

COVID-19 has caused unprecedented disruption in the way healthcare is delivered and received. Changes include decreases in in-person healthcare visits, delays in diagnosis and initiation of treatment, use of telemedicine, and changes in treatments and their monitoring.

The psychological and behavioral impact of the COVID-19 pandemic on the health environment is only now emerging.

In Obstetrics-Gynecology, perhaps more than in other specializations, we address a population of women who are as strong as they are vulnerable, namely pregnant women. Under this impetus, this thesis was developed, trying to capture the mother-fetus dyad in a difficult period for all of humanity.

In the beginning of the doctoral thesis, I included the general part, which represents the current state of knowledge extracted from published studies and specialized literature. Being a subject in continuous development and debate, I tried to capture all aspects of the SARS-CoV-2 infection and its impact on the obstetric population.

The special part represents a prospective study that captures the maternal-fetal complications through the prism of the clinical and paraclinical parameters studied and, last but not least, it aims at the quality of life of these patients. The first chapter of the special part is represented by a short introduction, followed by the Purpose and objectives of the research. The research methodology (Chapter V) includes a set of tools used in the realization of this thesis.

Chapter VI is the largest and most complex and is composed of the results of the research program carried out for the elaboration of this thesis. The results are structured in sub-chapters according to the particularities studied, so as to answer all the objectives the work.

Chapter VII includes the Discussions that create a parallel between the doctoral thesis and the specialized literature, going through the main aspects addressed in the paper. Similarities between the obtained results are outlined and different aspects are emphasized.

In Chapter VIII, the Conclusions are drawn, as a synthesis of the most important results obtained. Last but not least, the elements of novelty and personal contribution are taking shape.

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At the end of this stage in my life, at the end of the research activity within the Doctoral School, I have the honor to thank everyone who took part in this long process. Under the guidance of Prof. Dr. Marius Alexandru MOGA, I managed to carry out the entire research activity, the advice and indications given by him being a real landmark, for which I thank him. With deep respect, I would like to thank Mr. Prof. Dr. Aurel MIRONESCU, without whom the beginning of this research activity would not have been possible. I also thank the guidance committee, Conf. Univ. Dr. Costin Vlad ANASTASIU and Dr. Med. Petrina Rossana APOSTU, for the advice given throughout the development of the thesis and last but not least to the thesis evaluation committee, for the effort to evaluate my thesis.

I would like to thank the Transilvania University of Brașov and especially the Doctoral School for accepting me in the doctoral program and for the chance to complete this research.

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GENERAL PART

Chapter I. INTRODUCTION

The novel coronavirus SARS-CoV-2 was first reported in December 2019 in Wuhan City, Hubei Province, China. Doctors noted cases of pneumonia of unknown origin, which were later characterized as being caused by a new betacoronavirus. (Pedersen & Ho, 2020) Within months, SARS-CoV-2 has become a global emergency resulting in a wide spectrum of diseases, from asymptomatic infections to severe respiratory failure. The disease caused by SARS-CoV-2 was named COVID-19.

SARS-CoV-2 is an enveloped single-stranded RNA (genome size of 30 kb), consisting of four structural proteins (spike surface glycoprotein, coat protein, membrane protein and nucleocapsid protein) and non-structural proteins that are active targets of ongoing vaccine research. (Tung Thanh Le, 2020) (Ahmed et al., 2020) SARS-CoV-2 has over 80% similarity to SARS-CoV 4, 5, 6 which caused an outbreak in 2002 and shares 50% sequence similarity from the Middle East respiratory syndrome coronavirus (MERS) that caused an outbreak in 2012. (H. Wang et al., 2020) The mortality rate of SARS-CoV-2 is low compared to SARS and MERS; however, about 1% of infected people develop severe acute respiratory distress syndrome (ARDS) that requires a critical level of care. While the routes of transmission of SARS-CoV-2 remain under active investigation, the predominant methods are currently believed to be via aerosols and from surfaces. (Pedersen & Ho, 2020) Although much of the world is focused on the lethal respiratory effects of COVID-19, particularly in the elderly, emerging information suggests that COVID-19 puts young women and their children at increased risk for pregnancy complications . For example, in the majority of studies that included pregnant women infected with COVID-19, nearly 50% of them gave birth prematurely, and infected women had higher rates of pre-eclampsia and premature rupture of membranes than women without uninfected. (D. Di Mascio et al., 2020) (Zaigham & Andersson, 2020) Whether this virus can be transmitted vertically during pregnancy remains under investigation; however, its presence in the placenta and breast milk has already been documented in several recent studies. (Algarroba et al., 2020; Hosier et al., 2020) (Bastug et al., 2020; Khalil et al., 2020) The mechanisms underlying the effects of COVID-19 on pregnant women are also unknown and are under investigation.

Physiological changes that occur during pregnancy, including changes in immunity, can increase susceptibility to viral infections. In addition, the immature innate and adaptive immune system of the developing fetus makes them highly susceptible to infection with potentially deleterious consequences for fetal and neonatal brain development and function. Given the rapid spread of SARS-CoV-2 globally, it is important to understand the immediate and long-term risks of the virus to the mother-child dyad.

Chapter II. CURRENT STATE OF KNOWLEDGE REGARDING SARS COV 2 INFECTION

II.1. History and epidemiology

Humans have witnessed three deadly pandemics so far in the 21st century that are associated with novel coronaviruses: SARS, Middle East Respiratory Syndrome (MERS), and COVID-19. All these viruses, which are responsible for causing acute respiratory tract infections, are highly contagious in nature with high mortality. The newly emerging disease COVID-19 is a highly transmissible viral infection caused by another novel zoonotic coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Similar to the other two coronaviruses, such as SARS-CoV-1 and MERS-CoV, SARS-CoV-2 is likely to have originated from bats, which have served as stable reservoirs for various coronaviruses. Although it is not yet known how SARS-CoV-2 is transmitted from bats to humans, rapid human-to-human transmission has been widely confirmed. The disease first appeared in Wuhan, China in December 2019 and quickly spread across the globe, infecting 48,539,872 people and causing 1,232,791 deaths in 215 countries, and the infection is still spreading. (Khan et al., 2020)

The origin of COVID-19 is believed to be a wholesale seafood market in Hunan, which also sells various types of wild animals, including snakes, birds, bats, rabbits and frogs, etc. Sequence analysis of different coronavirus species revealed that SARS-CoV-2 is a recombined virus between the bat coronavirus and a coronavirus from an unknown source, which is suspected to be the pangolin. (Zheng, 2020) After the official declaration of the novel SARS-CoV-2 as a potential cause of the outbreak of COVID-19 in Wuhan, China, the most critical question in the minds of governments and public health officials was the possibility that SARS-CoV -2 to cause a global pandemic. A pandemic affects various aspects of health systems and requires extensive planning regarding supply, availability of human resources and ensuring the sustainability of the health system throughout the epidemic. (J. T. Wu et al., 2020) Moreover, drastic measures were needed to limit the pandemic. For example, implementing strict social distancing and mobility restrictions, such as closing schools, public offices, gardens, etc. and strict travel advisories/bans, which seriously disrupt social and economic stability.

As of March 10, over 48,000 confirmed cases and ~3,000 deaths have been reported across the globe. Finally, the WHO declared COVID-19 as a pandemic on March 11, 2020. (Whitworth, 2020) In particular, after March 15, there was a sharp increase in the number of infected cases and the death rate, and by at the end of March, the number of confirmed people rose to over 640,000 and the death rate exceeded >18%. Initially, the largest number of cases were reported in China; however, by mid-March, Europe had more cases than anywhere else in the world, while cases of COVID had spread to more than 160 countries and territories involving six continents. So far, ministries of health, public health organizations, medical research centers

and other health agencies around the world have worked tirelessly to minimize the threat of this massive pandemic. However, not only has it proven to be a medical emergency, but it will be considered one of the greatest human tragedies after the Second World War. It has severely affected economic activities and had huge socio-economic effects with far-reaching implications for global trade, travel and supply chains, thus greatly disrupting the daily lives of people across the globe.

II.2. Structure of the SARS-COV 2 virus

The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has classified coronaviruses in the family Coronaviridae, subfamily Coronavirinae. Based on genotypic and serological characterization, Coronavirinae is divided into 4 genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. (Cui et al., 2019; Fung & Liu, 2019; Woo et al., 2012) Only 6 HCoV species that cause human disease were known before December 2019. Four of them cause common cold symptoms in immunocompromised individuals: these are HCoV-229E and HCoV-OC43, first identified in the mid-1960s (Hamre & Procknow, 1966; Kahn & McIntosh, 2005; Tyrrell & Bynoe, 1966); HCoV-NL63, first identified in 2004 (Fouchier et al., 2004; van der Hoek et al., 2004); and HCoV-HKU1, first identified in 2005. (Lau et al., 2006) The other 2 strains, which cause fatal disease, are SARS-CoV, first identified in 2003, and MERS-CoV, first identified in 2012. (Holmes, 2003; Zaki et al., 2012) SARS-CoV-2 has 96% of its nucleotide sequence identical to bat coronavirus RaTG13, a SARS-like coronavirus, therefore belongs to the genera Betacoronavirus.

The SARS-CoV-2 genome contains 4 structural proteins that are responsible for virus-host cell receptor binding, virion assembly, morphogenesis and release of virus particles from the host cell. The SARS-CoV-2 E protein is the smallest of all the structural proteins found in the viral membrane and localizes to the endoplasmic reticulum and Golgi complex in host cells. (Nieto-Torres et al., 2011) Protein E, together with M and N, is known to facilitate the formation of virus-like particles. Glycoprotein M is a transmembrane protein located in the viral membrane and is the most abundant structural protein in a virion, nearly one hundred times more abundant than protein E. Protein M plays a major role in viral assembly along with proteins E and N. (Siu et al., 2008; Vennema et al., 1996; Voss et al., 2006)The N protein is responsible for packaging the viral genome RNA (gRNA) into a helical ribonucleocapsid (RNP). SARS-CoV-2 also has 8 subgenomic RNA-derived accessory proteins: 3a, 3b, 6, 7a, 7b, 8b, 9b, and orf14, and they are distributed between structural genes. (C. Wang et al., 2020; A. Wu et al., 2020; Zumla et al., 2016)

Coronaviruses use an RNA-dependent RNA polymerase (RdRp) complex for genome replication and transcription of their genes. (Snijder et al., 2016) The SARS-CoV-2 RdRp complex is composed of a catalytic subunit nsp12 and two accessory subunits nsp7 and nsp8, which increase the binding and processivity of the RdRp template. (Subissi et al., 2014)

The S protein is a multifunctional molecular machine that plays key roles in the early stages of viral infection by interacting with host susceptibility factors, including receptors and proteases.

S proteins are clove-shaped type I transmembrane proteins and have 3 segments: a large ectodomain, a single-pass transmembrane, and an intracellular tail. The ectodomain of S proteins consists of the S1 subunit, which contains a receptor binding domain (RBD), and the membrane fusion subunit (S2). The recognition of the host cell receptor by the RBD on S proteins is the initial step of viral infection, and the binding interactions between the coronavirus tip and its receptor is one of the most critical factors for host cell and interspecies transmission. Human coronaviruses recognize a variety of host receptors; specifically, HCoV-229E recognizes human aminopeptidase N (hAPN) (Wentworth & Holmes, 2001), MERS-CoV binds to dipeptidyl peptidase-4 (DPP4) (Raj et al., 2013), HCoV-OC43 and HCoV- HKU1 binds certain types of O-acetylated sialic acid (Hulswit et al., 2019), and HCoV-NL63 and SARS-CoV recognize angiotensin-converting enzyme 2 (ACE2). (Li et al., 2003) Recent structures together with functional studies have suggested that SARS-CoV-2 S proteins use ACE2 and transmembrane serine protease type 2 (TMPRSS2) for host cell entry, which are very similar to the mechanisms exploited by SARS-CoV. (Hoffmann et al., 2020) S proteins, common among all coronaviruses, are a major target for eliciting antibodies; therefore, structural and molecular details of the S protein and its interactions with cognate receptors would be vital in the development of vaccines and antiviral drugs against SARS-CoV-2.l

II.3. Diagnostic methods of the COVID-19 virus

For more than two years, COVID-19 has spread rapidly in many countries, attracting global attention because the infection can be fatal. (Zhou et al., 2021) The coronavirus belongs to the coronaviridae family (Zhang et al., 2020b). Genome sequencing of the novel coronavirus isolated from patients' bronchoalveolar lavage fluids revealed 96% and 80% similarities to the genomes of bat coronavirus RaTG13 and severe acute respiratory syndrome virus (SARS-CoV), respectively. (Lu et al., 2020) This coronavirus is known as SARS-CoV-2.

Thanks to the development of molecular biology technologies, molecular diagnostic methods have developed rapidly. Among them, polymerase chain reaction (PCR)-based tests are considered the gold standard for virus detection due to their high sensitivity and specificity. (Shen et al., 2020) However, PCR-based detection has many limitations, such as the need for a high-purity sample, expensive laboratory equipment, specialist training, and long reaction time. (V. M. Corman et al., 2020) Other molecular diagnostic methods such as clustered regularly interspaced short palindromic repeats (CRISPR) and gene sequencing have the same drawbacks. Therefore, researchers have sought to develop alternative diagnostic methods, such as protein

testing and computed tomography. Each method has its own advantages, but also some limitations.

II.4. Symptoms of COVID-19 in pregnant women

Pregnant women do not appear to be more or less likely to contract the infection than the general population. (Docherty et al., 2020) The multinational INTERCOVID study of unvaccinated women showed that pregnant women with pre-existing diabetes, obesity and insulin-requiring gestational diabetes were significantly more likely to contract SARS-CoV-2 infection compared to pregnant women without these comorbidities. Women with diabetes have an almost double risk of SARS-CoV-2 infection (RR 1.94, 95% CI 1.55–2.42), overweight and obese women have a 20% increased risk (RR 1.20, 95% Cl 1.06–1.37) and women who developed insulin-dependent gestational diabetes are at increased risk of SARS-CoV-2 infection.

(RR 1.79, 95% CI 1.06–3.01). (Eskenazi et al., 2021)

Most pregnant women who are infected with SARS-CoV-2 are asymptomatic. The PregCOV-19 Systematic Review (John Allotey et al., 2020) created a report on universal screening during pregnancy and found that approximately 73% (95% CI 62–82) of women were asymptomatic, while another US study reported that 86% of women admitted to labor who tested positive for SARS-CoV-2 were asymptomatic. (Reale et al., 2021) Most symptomatic women experience only mild or moderate cold/flu symptoms. The PregCOV-19 systematic review (John Allotey et al., 2020) included more than 64,000 pregnant women worldwide with suspected or confirmed COVID-19. In this review the overall rate of diagnosis of COVID-19 in pregnant women admitted to hospital for any other reason was 10%. The most common symptoms of COVID-19 in pregnant women were cough (41%) and fever (40%). Uncommon symptoms were dyspnoea (14%), myalgia (15%), loss of taste (11%) and diarrhea (6%).

Pregnant women with COVID-19 were less likely to have fever or myalgia than non-pregnant women compared to age-matched women. The PRIORITY study (Pregnancy CoRonavirus Outcomes RegiIsTry) an ongoing prospective cohort study of pregnant women in the US found that among the first predominant symptoms in infected women were cough (20%), sore throat (16%), myalgias (12%) and fever (12%). In this group of 594 symptomatic women, a quarter had persistent symptoms 8 weeks or more after onset. (Afshar et al., 2020)

It is currently unclear whether pregnancy will have an impact on the percentage of women who develop prolonged signs and symptoms after an acute SARS-CoV-2 infection, the so-called "long-lasting COVID" or post-COVID-19 state. The National Institute for Health and Care Excellence (NICE) has produced a quick guide highlighting the care of people who develop the long-term effects of COVID. (Knight et al., 2020)

The Omicron variant may be associated with less severe disease than the Delta variant, but is more infectious and likely associated with maternal and neonatal adverse effects, particularly in unvaccinated pregnant women.

In conclusion, it can be stated that:

- Pregnant women without comorbidities have the same risk of contracting the infection as the general population.
- Pregnant women with comorbidities such as pre-existing diabetes, body mass index (BMI) > 25 kg/m2, insulin-requiring gestational diabetes have an increased risk of SARS-CoV-2 infection.
- Most pregnant women who are infected with SARS-CoV-2 are asymptomatic.
- Most symptomatic women have only mild or moderate cold/flu-like symptoms.
- The main symptoms of COVID-19 in pregnancy are cough, fever, sore throat, dyspnea, myalgia, loss of taste and diarrhea.

II.5. The effect of COVID-19 on pregnancy

Preterm birth is the biggest cause of neonatal morbidity and mortality in the UK, with a rate of around 7% of babies born prematurely. The rate of preterm births in women with symptomatic COVID-19 appears to be two to three times higher than the background rate. (D'Onofrio et al., 2013)

The PregCOV-19 systematic review estimated the risk of preterm birth to be approximately 17%. The majority of these preterm births (94%) were iatrogenic. In the original UKOSS study,29 the median gestational age at delivery was 38 weeks' gestation (IQR 36–39 weeks' gestation). (J. Allotey et al., 2020)

Of the women who gave birth, 27% had preterm births: 47% of these were iatrogenic in maternal interest and 15% were iatrogenic in fetal interest. The updated UKOSS study confirmed that preterm birth was more likely for women with COVID-19: 19% of women with symptomatic COVID-19 and 9% of women with asymptomatic COVID-19 gave birth before 37 weeks' gestation. Compared with a cohort of pregnant women without SARS-CoV-2, pregnant women with symptomatic COVID-19 were more likely to deliver before 32 weeks' gestation (adjusted OR [aOR] 3.98, 95% CI 1 .48–10.70) and before 37 weeks of gestation (aOR 1.87, 95% CI 1.23–2.85). (Vousden et al., 2021)

Subsequent studies have confirmed the increased risk of preterm birth in mothers with symptomatic COVID-19 infection. Pregnant women with asymptomatic COVID-19 do not, however, appear to have a significantly increased risk of preterm birth. (Cruz-Lemini et al., 2021)

A published systematic review of 42 studies reported an increased risk of low birth weight (OR 1.89, 95% CI 1.14-3.12) associated with maternal COVID-19 infection and another multinational study reported , also a higher rate of low birth weight (RR 1.58, CI 95% 1.29–1.94) among women infected with COVID-19. This evidence adds to the possibility that maternal infection with COVID-19 causes IUGR. (Villar et al., 2021; Wei et al., 2021)

For children born to women with COVID-19, overall outcomes are favorable, with more than 95% of newborns included in the PregCOV-19 systematic review reporting that they were born well. (J. Allotey et al., 2020) A large US study also reported reassuring results regarding newborns during the pandemic. Of the total of 1481 births, 116 (8%) women (who gave birth to 120 newborns) tested positive for SARS-CoV-2. All 120 newborns were tested at 24 hours of life, none were positive for SARS-CoV-2. Of 79 newborns who were retested for SARS-CoV-2 5–7 days after birth (66% follow-up rate), all tests were negative; 72 newborns were also tested at 14 days, none were positive. None of the newborns had signs of COVID-19. (Salvatore et al., 2020)

Despite more than 100 million confirmed COVID-19 infections worldwide, no increase in the incidence of birth defects has been reported.

There is evidence that COVID-19 infection causes a number of nonspecific placental histological abnormalities, including fetal and maternal vascular changes, malperfusion, chorioamnionitis, acute inflammatory pathology, chronic inflammatory pathology, and intervillous thrombosis. Studies have described specific histological features of placentas associated with cases of stillbirth and late second-trimester miscarriage related to infection with both the Alpha and Delta variants. Severe placental lesions proven in the setting of placental infection with COVID-19, such as trophoblastic necrosis and massive hemorrhage, causing rapid deterioration of placental function have been linked to a number of stillbirths in women infected with COVID-19. (Dubucs et al., 2022; Fitzgerald et al., 2022) In another study, 10 of 50 placentas from unvaccinated, positive, COVID-19 women showed evidence of placental infection. Five of these were associated with stillbirths with severe placental changes, while the remaining five had more focal changes in association with possible IUGR. (Dubucs et al., 2022) Another study showed the same histological findings for placental infection associated with COVID-19 (Alfa variant), which resulted in six stillbirths, all attributable to placental insufficiency, three of which were associated with coagulation abnormalities, and three of them showed reduced fetal movements in the days before birth. (Fitzgerald et al., 2022) Both studies reported that placental changes leading to stillbirth did not correlate with the severity of the woman's COVID-19 symptoms, with most having only mild symptoms. IUGR was not a feature in these cases so these histological changes resulted in rapid placental dysfunction and stillbirth. Therefore, it is possible that severe placental dysfunction may occur relatively suddenly, which appears to be unrelated to the severity of symptoms, but to placental infection with COVID-19. It may be associated with a coagulopathy similar to disseminated intravascular coagulation (DIC),

characterized by low platelet count and low fibrinogen, and is strongly associated with a severe perinatal outcome.

There is less data available on the impact of COVID-19 infection on first and second trimester pregnancy loss. A nationwide study in the US reported no increased risk of fetal loss before 20 weeks' gestation due to COVID-19 infection.

Maternal COVID-19 is associated with an increased rate of cesarean deliveries. According to the UKOSS study, 59% of women gave birth by caesarean section; approximately half of these were of maternal or fetal interest. The rest were for obstetric reasons (eg, lack of progression of labor, previous cesarean delivery) or maternal demand (6%). Among women who gave birth by caesarean section, 20% required general anesthesia (GA). About two-thirds of women who had general anesthesia were intubated because of maternal respiratory distress, and the remaining one-third to facilitate emergency delivery. (Knight et al., 2020)

Thus it can be stated that:

- Symptomatic maternal COVID-19 is associated with an increased likelihood of iatrogenic preterm birth.
- Infection with COVID-19 during pregnancy may be associated with an increased incidence of small for gestational age (SGA) infants.
- Neonatal morbidity for children born to women with COVID-19 appears to be related to preterm birth rather than to the COVID-19 infections themselves.
- While stillbirth remains a rare phenomenon, maternal infection with COVID-19 is associated with an increased risk of stillbirth.

II.6. Vaccination of COVID-19 in pregnancy

Background of the COVID-19 vaccine (in the non-pregnant population):

- Phase 3 studies of the four currently approved vaccines evaluated protection against COVID-19 after two of three doses and after a single dose.
- Before the appearance of the Omicron variant of COVID 19:
    - The Pfizer-BioNTech vaccine was 95% (95% CI 90.0–97.9%) effective against symptomatic COVID-19. (F. P. Polack et al., 2020)
    - The Oxford-AstraZeneca vaccine was 66.7% (95% CI 57.4– 74.0%) effective against symptomatic COVID-19. (Voysey et al., 2021)
    - The Moderna vaccine had an efficacy of 94.1% (95% Cl 89.3–96.8%). (Baden et al., 2020)
    - The Janssen vaccine had an efficacy of 66.1% (95% CI 55.0–74.8%). (Sadoff et al., 2021)

- Real-world monitoring has confirmed that one dose of Pfizer-BioNTech or Oxford-AstraZeneca Vaccines provides approximately 60% protection against symptomatic COVID-19 (Alpha and Delta variants), however it provides less protection against the Omicron variant. (Bernal et al., 2020)
- Real-world monitoring has confirmed that one dose of Pfizer-BioNTech or Moderna Vaccines confers approximately 75% protection against symptomatic COVID-19 which drops to 25% after 25 weeks. Two doses of the Oxford-AstraZeneca vaccine confer about 45–50% protection against Omicron, which is almost ineffective after 20 weeks. (Agency)
- A booster dose of Pfizer-BioNTech or Moderna gives about 60–75% protection against Omicron, which drops to 25–40% after 15 weeks.
- Vaccination with two doses of Pfizer-BioNTech or Oxford-AstraZeneca vaccines are effective against symptomatic diseases secondary to infection with the Delta variant (Abu-Raddad et al., 2021)
- Those who received two doses and a booster (or three doses) of the vaccine (combined data on Pfizer-BioNTech, Oxford-AstraZeneca and Moderna) are 88% less likely to be hospitalized with the Omicron variant than those who did not was vaccinated. (Agency)
- Women should be informed that influenza vaccination is safe and recommended during pregnancy to protect both the woman and the baby from the adverse effects of serious influenza illness during pregnancy.
- Women can get the COVID-19 and flu shots at the same time.

II.7. Types of vaccines available in Romania

As of February 2022, four COVID-19 vaccines are approved for use in Romania: the PfizerBioNTech vaccine, the Oxford-AstraZeneca vaccine, the Moderna vaccine, the Janssen vaccine.

The Pfizer-BioNTech and Moderna vaccines are messenger RNA (mRNA) vaccines in which the mRNA encoding the SARS-CoV-2 spike protein is injected through a lipid nanoparticle coating. The mRNA does not enter the host cell's nucleus, so it remains separate from the host's DNA. The vaccine mRNA is broken down by the host cell within days.

The Oxford-AstraZeneca and Janssen vaccines are viral vector vaccines in which DNA encoding the SARS-CoV-2 spike protein is injected into a modified adenovirus vector. The adenovirus vector has been modified so that it cannot replicate, and the spike protein is not expressed on the adenovirus itself. Rather, the adenovirus vector serves only to release and introduce protein DNA into the host cell. The host cell then produces the spike protein and this triggers a protective immune response.

Current vaccines against COVID-19 offer a lower degree of protection against Omicron, with the level of protection declining more rapidly in the months after vaccination. (Ren et al., 2022)

However, vaccination protects people against symptomatic coronavirus and decreases hospitalization.

UKHSA data demonstrated the importance of a booster dose for protection against the Omicron variant. For example, a Pfizer-BioNTech or Moderna booster after two initial doses of the Oxford-AstraZeneca or Pfizer BioNTech vaccines increased protection against symptomatic Omicron infection from 0–10% pre-booster protection to 50–80% at one week. Protection levels of approximately 40-70% persisted 10 weeks after the booster dose depending on the exact vaccination regimen administered.

II.8. Placental physiology and interaction with SARS-CoV-2 infection

The role of the placenta in SARS-CoV-2 infection is poorly understood. Although it appears that vertical transmission to the fetus can occur, the mechanisms underlying this type of transmission are uncertain.

The placenta is usually an effective barrier that prevents maternal infection from spreading to the fetus through vertical transmission. It is well recognized that certain pathogens can overcome this barrier and have sometimes devastating effects on the developing pregnancy. (Coyne & Lazear, 2016) Cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus and Zika virus (ZIKV) can cause congenital syndromes, with variable rates of transmission and severity, and the effects depend, in part, on age the pregnancy in which the infection occurs. Many of these infections may have only minor effects on the mother, and the correlation between maternal symptomatology and the severity of fetal effects is poorly recognized. The experience of viral infections during pregnancy has led to three key observations regarding congenital infections. First, the presence of virus on the placental surface does not necessarily indicate placental infection—vertical transmission of viruses depends on the occurrence of breaches in the placental barrier. Second, viral infection of placental cells does not necessarily mean that there is transmission to the fetus. Third, even when fetal infection occurs, responses are heterogeneous; thus, fetal infection does not always mean fetal damage.

The human placenta is hemochorial, meaning the maternal blood is in direct contact with the placental chorionic villi. The placenta consists predominantly of cells called trophoblasts, of which there are three main types: multinuclear syncytiotrophoblast cells - line the villus shaft and are in direct contact with maternal blood; villous cytotrophoblast - the cells that form the basis of the syncytiotrophoblast, invasive extravillous cells - trophoblast cells that anchor the chorionic

villi of the uterus and change its vascularity. A number of potential mechanisms may be involved in the vertical transmission of viruses:

- direct damage to the villous shaft, with breaks in the protective syncytiotrophoblast layer;
- viral spread from the infected maternal endothelium to the extravillous trophoblast;
- transport of infected maternal immune cells via syncytiotrophoblast or paracellular or transcellular transport (eg, immunoglobulin-mediated transcytosis) into fetal capillaries;
- ascending infection from the vagina. (Coyne & Lazear, 2016)

There have been a number of case reports examining the placenta of women with COVID-19. SARS-CoV-2 expression was detected in midtrimester placental samples, but it remains unclear whether the presence of the virus was due to the primary infection or was facilitated by placental damage from other pathologies. SARS-CoV-2 was found on RT-PCR and biopsy from a spontaneously aborted fetus at 19 weeks of gestation. (Whittaker et al., 2020) SARS-CoV-2 was also highly detected in placental and umbilical cord biopsies from a pregnancy following termination at 22 weeks of gestation. (Mao et al., 2022) The pregnancy was terminated due to placental abruption and severe maternal preeclampsia with thrombocytopenia and coagulopathy. In this case, electron microscopy revealed virus-like particles in the cytosol of placental cells, however, no viral expression was detected in the fetal tissues tested. In both cases, macrophages infiltrate, and fibrin deposits were observed on placental histology, which the authors attributed to be most likely associated with viral infection. (D. Baud et al., 2020) However, such intervillosis may also be idiopathic, autoimmune, or associated with other infections, and thus may not be related to the presence of SARS-CoV-2. In another case studied, both placental and amniotic fluid positive tests for SARS-CoV-2 were identified. On microscopic examination, the placenta also had evidence of perivillocytic fibrin deposition with infarcts and intervillosis. In this case, the newborn tested positive on nasal and rectal tests, and required NICU for respiratory support. (Vivanti et al., 2020)

Two other publications report placental histological findings in women with SARS-CoV-2 infection. In another study of placentas from 20 women, they were found to be positive for SARSCoV-2 in routine tests at the time of delivery (32 to 40 weeks gestation), of which 10 placentas showed signs of possible fetal vascular malperfusion or fetal vascular thrombosis. (Baergen & Heller, 2020)

Another study examined placentas from 16 women with SARSCoV-2 infection, 11 of whom were diagnosed near birth and 5 were diagnosed earlier. (Shanes et al., 2020) Placentas were from pregnancies between 16 and 40 weeks' gestation. Twelve of 15 third-trimester placentas were reported to have signs of maternal vascular malperfusion such as villous infarcts, agglutinated villi, or decidual arteriopathy. Histopathological examination was indicated in the context of maternal SARS-CoV-2 infection in most cases, and histological signs of placental vascular malperfusion are somewhat subjective, so these findings should be interpreted with caution. Further research is needed, including standardized examination of placental samples from women with SARS-CoV-2 by pathologists unaware of the mother's infection status. In

addition, these findings should be correlated with the clinical status of the fetus, ideally with long-term follow-up. (Kreis et al., 2020)

II.9. Vertical transmission of SARS-CoV-2

Viral infection of placental cells does not necessarily mean fetal infection or fetal harm. To date, 15 reports include neonatal test results for SARS-CoV-2 (Breslin et al., 2020; R. Chen et al., 2020; Ferrazzi et al., 2020), with positive cases occurring in a number smaller. (Marín Gabriel et al., 2020; N. Yu et al., 2020)

Significant neonatal respiratory disease appears to be rare, even in the presence of a positive test for SARS-CoV-2. It is unclear from PCR-based SARS-CoV-2 test reports whether infection occurs in utero or during labor or delivery; or if transmission occurs from the infected mother or asymptomatic hospital staff. But the availability of antibody tests has provided new evidence that vertical transmission can occur. Some babies born to mothers with COVID-19 have elevated concentrations of both immunoglobulin (Ig) M and IgG to SARS-CoV-2. Although IgG can be passively transferred from mother to fetus in utero, IgM has a higher molecular weight and cannot cross the placenta. Circulating SARS-CoV-2 IgM in the neonate therefore indicates vertical transmission of the virus, although all infants in the reports so far were asymptomatic and tested negative for SARS-CoV-2 viral RNA at birth. (H. Zeng et al., 2020)

The mechanisms of viral invasion of the placenta are not yet clearly established. In the lungs, SARS-CoV-2 uses the ACE2 receptor to enter cells and the serine protease TMPRSS2 is involved in cleaving the spike glycoprotein to allow fusion. Three studies analyzed single-cell RNA sequencing data to determine whether ACE2 + /TMPRSS2 are expressed on placental cells. Li et al. performed a secondary analysis of single-cell transcriptome profiles available from decidua and placenta samples at 6–12 weeks' gestation, with additional data from a previous study of two term placenta samples. (M. Li et al., 2020) ACE2 gene expression has been reported in first trimester decidual stromal and perivascular cells, and villous cytotrophoblast and syncytiotrophoblast in both first trimester and term samples. However, another study using the same data set for the first trimester found only very low expression of ACE2 in placental and decidual cell populations. (L. Zhang et al., 2020)

An additional study looked at human embryos to investigate possible routes of transmission in the first trimester and found ACE2 expression and co-expression of TMPRSS2 in the trophoblast, blastocyst and hypoblast, suggesting that fetal infection via this route is possible. (Weatherbee et al., 2020)

Given the lack of coexpression of ACE2 and TMPRSS2 in the placenta, it therefore seems likely that SARS-CoV-2 enters placental tissues by an alternative mechanism. A number of other proteases have also been implicated. DPP4 and CD147 are both highly expressed in the

placenta throughout gestation and may have a role in cell entry. (Kreis et al., 2020) Furin, trypsin and cathepsins B and L have been shown to have the ability to cleave the peak glycoprotein and bind to the S1/S2 site. In addition, plasmin can cleave this site and has been identified as a possible therapeutic target with tranexamic acid to prevent cell entry. SARS-Cov-2 viral RNA was detected in amniotic fluid in cases of severe maternal disease, although neonatal positivity at birth was variable. (Mao et al., 2022)

Pregnant women infected with SARS-CoV-2 are susceptible to pneumonia and preterm birth before <37 and 34 weeks of gestation, and the risk of miscarriage in early pregnancy may be increased. (D. Di Mascio et al., 2020) (C. Huang et al., 2020; Zaigham & Andersson, 2020) Liu et al., reported that in a cohort of 13 pregnant women infected with COVID-19, nearly 50 % (6/13) gave birth prematurely. (Y. Liu et al., 2020) Zeng et al., described cases of early-onset neonatal infection in a cohort study of 33 pregnant women in Wuhan with confirmed SARS-CoV-2 and identified the infection status and clinical course of newborns. Of the 33 newborns, 3 tested positive for SARS-CoV-2 and had symptoms of COVID-19, including fever, respiratory distress syndrome, or difficulty breathing. All three neonates were delivered by caesarean section due to uncertain fetal status. This study concluded that, given the strict infection control and SARS-CoV-2 IgM. The presence of IgM suggested maternal-fetal transmission of antibodies, but the child did not develop any symptoms of COVID-19. (L. Zeng et al., 2020) A systematic review and meta-analysis that analyzed data from 17 studies, including 2567 pregnancies, identified the most common causes of SARS-CoV-2 infection as preterm birth iatrogenic and cesarean delivery. The incidence of perinatal deaths was observed to be less than 1% (12 stillbirths and 4 neonatal deaths), and 1%–2% of newborns were positive for SARS-CoV-2. (Khalil et al., 2020)

However, other studies have concluded that there is no evidence of vertical transmission. For example, one study demonstrated that in a cohort of 9 women who were confirmed to have COVID-19 pneumonia, no children tested positive for SARS-CoV-2 via amniotic fluid, umbilical cord blood, throat or breast milk. (Juan et al., 2020) (H. Chen et al., 2020) Another study with 38 pregnant women infected with SARS-CoV-2 in the third trimester of pregnancy reported no maternal deaths or cases of vertical transmission to newborn after testing all neonatal samples and some placentas for SARS-CoV-2. (Schwartz, 2020) Huntley et al., reviewed 13 studies comprising 538 pregnancies and reported neonatal death in 0.3% (1/313) of newborns and no vertical transmission. (Huntley et al., 2020) Chen et al., reported a 20% incidence of preterm birth in 118 pregnancies, but no vertical transmission. (Huntley et al., 2020) The preponderance of evidence so far does not indicate a significant role for vertical transmission, but it remains a goal to understand the impact of COVID-19 on maternal morbidity and mortality.

II.10. Immunology of COVID-19 in pregnancy

Pregnancy is an immunological condition in which the semi-allogeneic fetus grows in the mother's womb. The immunologic milieu during pregnancy changes as the pregnancy initially shifts through Th1 (pro-inflammatory response) during the first trimester, then shifts to Th2 (anti-inflammatory response) by the second trimester and polarizes again to a Th1 phenotype at the end of the third trimester simultaneously with the onset of labor. (Mor et al., 2017) In addition, the number of immune cells also varies during pregnancy, with a higher prevalence of innate immune cells (NK cells, monocytes) than adaptive immune cells (fewer B and T cells). (Mor et al., 2017) SARS-CoV-2 infection appears to induce a reduction in the number of lymphocytes compared to inflammatory monocytes, which could induce a cytokine storm leading to acute respiratory distress syndrome and multi- - systemic organs. (Villar et al., 2019) (Channappanavar & Perlman, 2017) In support of this hypothesis, plasma from severely infected COVID-19 patients showed increased levels of interleukins (IL-2, IL-6, IL- 7 and IL-10), granulocyte colony-stimulating factor (GCSF), interferon-γ -inducible protein 10 (IP-10 or CXCL10), monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α) and tumor necrosis factor α (TNF-α). (Channappanavar & Perlman, 2017; C. Huang et al., 2020; Tetro, 2020) High level of TNF-α during pregnancy is associated with defects in early embryo development. (Yockey & Iwasaki, 2018) (Fried et al., 2017) A recent systematic review identified elevated C-reactive protein (CRP) in most pregnant women positive for COVID-19. (Juan et al., 2020) Taken together, the cytokine storm (pro-inflammatory cytokines) induced by SARS-CoV-2 could put pregnant women at greater risk by causing an increased pro-inflammatory state with the potential to affect brain development fetal, thus increasing the risk of autism, mental health disorders or schizophrenia. (Mor et al., 2017) (Al-Haddad et al., 2019) (Shi et al., 2005)

Currently, there are no reported studies on the interactions of decidual immune cells with SARS-CoV-2, but there are studies on the effect of SARS-CoV-2 on peripheral blood leukocytes. A key difference observed in peripheral blood leukocytes in those with severe symptoms of COVID-19 compared to those with mild symptoms was a decrease in IFN-γ and TNF-α in CD4+ T cells in the severe symptoms group. In addition, increased levels of granzyme B and perforin were observed in CD8+ T cells. (Zheng et al., 2020) This study also found an increase in CD8+ T cell depletion in the severe group, suggesting that CD8+ T cell depletion may affect patients' ability to mount an adequate immune response to SARS-CoV- 2. (F. Wang et al., 2020; Zheng et al., 2020) Associated lymphopenia in patients with confirmed SARS-CoV-2 has also been widely reported. (D. Wang et al., 2020) Whether there is an alteration of decidual NK cell or T cell populations at the maternal-fetal interface in COVID-19-positive placentas remains to be determined.

II.11. Immunological mechanisms of SARS-CoV-2 infection on pregnancy loss

II.11.1. SARS-CoV-2 infection

The SARS-CoV-2 virus is a positive-strand enveloped RNA virus. There are approximately 29 different viral proteins identified; the most important are the nucleocapsid (N), membrane (M), spike (S) and envelope (E) proteins. The capsid was formed outside the genome by the N protein, and the genome is further wrapped by an envelope associated with structural proteins (M protein, S protein, and E protein). (M. Y. Wang et al., 2020) Angiotensin-converting enzyme 2 (ACE2) is the host receptor for SARS-CoV-2 cell entry. S proteins are evenly distributed on the surface of the virus, allowing greater interaction with ACE2. After binding to ACE2, cellular transmembrane serine protease 2 (TMPRSS2), located on the host cell membrane, promotes virus entry into the cell by activating protein S. (M. Y. Wang et al., 2020)

Initially, SARS-CoV-2 infects nasal epithelial cells and then spreads to bronchial epithelium and alveolar type II epithelial cells, which express ACE2 and TMPRSS2. After reaching pneumocytes, in moderate/severe forms of COVID-19, intense viral replication occurs, triggering local and systemic immune responses. (M. Y. Wang et al., 2020) Transmission and severity of COVID-19 appear to be related to viral load in the upper and lower respiratory tract, respectively. (Cevik et al., 2021) Typically, viral respiratory pneumonia with critical hypoxemia is the most common clinical manifestation of severe COVID-19. During the acute phase of the disease, COVID-19 usually affects other organs, either directly or through systemic complications of the intense pulmonary inflammatory response known as cytokine storm. (M. Y. Wang et al., 2020)

II.11.2. Effects of SARS-CoV-2 infection during pregnancy

Studies have shown that a variety of extrapulmonary organs are potential targets for SARS-CoV-2. In addition, ACE2 proteins are expressed in various organs such as the heart, kidney, liver, digestive tract, and brain. (Dong et al., 2020) For decades, researchers have described the expression of ACE2 and TMPRSS2 in the endometrium, embryo, and various cell types of the human placenta, including syncytiotrophoblast, cytotrophoblast, invasive and intravascular trophoblast, decidual cells, vascular smooth muscle of primary villi and arterial and venous umbilical endothelium. (Valdés et al., 2006a; Vaz-Silva et al., 2009; Weatherbee et al., 2020) Recently, ACE2 and TMPRSS2 expression was detected in the human trophectoderm in early embryos as well as in all three trimesters of pregnancy. (Cui et al., 2021) On the other hand, ACE2 and TMPRSS2 expression was negatively correlated with gestational age, with ACE2 and TMPRSS2 being highly expressed in first-trimester trophoblast tissues and poorly expressed or undetectable in third-trimester placenta. (Bloise et al., 2021)

Therefore, the preconception and early pregnancy uterine environments are potentially vulnerable to SARS-CoV-2 infection. Thus, the appearance of COVID-19 in the periconceptional period can increase the risk of spontaneous abortion.

The renin-angiotensin system (RAS) is composed of a set of peptides, enzymes and receptors involved in the pregnancy process. RAS components are distributed throughout the uteroplacental unit. Angiotensinogen, renin, ACE, angiotensin I, angiotensin II, and angiotensin receptors (type 1 and type 2) are found in the placenta, uterus (endometrium and myometrium), fetal membranes, and amniotic fluid. In early pregnancy, high estrogen levels stimulate hepatic production of angiotensinogen, thereby increasing plasma and uterine levels. Studies have shown that RAS changes are linked to obstetric complications such as preeclampsia. (Anton & Brosnihan, 2008; Qi et al., 2020)

ACE2 and TMPRSS2 are highly expressed in human endometrial stromal cells during the secretory phase and are required for decidualization of human endometrial stromal cells. (Vaz-Silva et al., 2009) In addition, ACE2 is also an important component of the human placental renin-angiotensin system (RAS), which is upregulated in the first trimester and is involved in endometrial neovascularization during the peri- implantation as well as in placental development. (Qi et al., 2020) During pregnancy, placental RAS expression is decreased. When women with recurrent miscarriage were compared with fertile women, the expression of RAS components was found to be dysregulated. (Qi et al., 2020) The SARS-CoV-2-ACE2 complex negatively regulates ACE2, leading to a decrease in plasma angiotensin-(1–7) levels, which in turn potentiates vasoconstriction and the hypercoagulable state, contributing to reproductive failure and other obstetric complications. (Narang et al., 2020)

II.12. SARS-CoV-2 infection and pregnancy loss

Increased risk of embryo implantation failure and miscarriage has been reported in the periconceptional period in women with COVID-19. It was speculated that the reproductive failure was due to systemic inflammation and interference with trophectoderm-endometrium molecular signaling, rather than a direct action of SARS-CoV-2 at the implantation site. (Sills & Wood, 2020)

The immunopathology of COVID-19, accompanied by high levels of IL-6, IL-8, TNF-alpha and other cytokines, would lead to imbalanced Th1/Th2 immune responses. Consequently, the "cytokine storm" of COVID-19 induces a hypercoagulable state that is detrimental to normal blastocyst/fetus development in utero (toxic endometrial microenvironment and hypoperfusion secondary to microthrombi formation), as well as an unfavorable uterine immune response to embryo implantation . (Sills & Wood, 2020) Indeed, abnormalities of the maternal immune response during periimplantation and early pregnancy, with a predominant proinflammatory

response (Th1 and Th17) and thrombophilic states have been linked to recurrent implantation failure and miscarriage. (Kwak-Kim et al., 2014; H. Liu et al., 2020; Yang et al., 2010)

SARS-CoV-2 has been found in various body fluids, including blood, cerebrospinal fluid, pericardial fluid, pleural fluid, urine, semen, saliva, and eye tissues. (Bora et al., 2020; Chang et al., 2020; Farina et al., 2020; Y. H. Huang et al., 2020; Mei et al., 2020; Moriguchi et al., 2020; W. Wang et al. , 2020) plasma SARS-CoV-2 RNA was detected in 27% of hospitalized participants and 13% of outpatients with COVID-19. In addition, the viral load (measured by a nasopharyngeal swab, oropharyngeal saliva or aspirate, or endotracheal plasma) of patients with COVID-19 was associated with disease severity (worse severity of respiratory disease, lower absolute lymphocyte counts, and increased markers of inflammation, including C-reactive protein and IL-6) and mortality. (Fajnzylber et al., 2020) Although the dynamics of SARS-CoV-2 during the active phase of the disease remains to be elucidated, endometrial, decidual and placental infection is possible through hematological spread of SARS-CoV-2. Indeed, placental SARS-CoV-2 infection has been described by molecular and immunohistochemical tests as well as by electron microscopy. The presence of SARS-CoV-2 was confirmed in a 22-week placenta, being located primarily on syncytiotrophoblast cells at the maternal-fetal interface. (Hosier et al., 2020)

According to a recent meta-analysis by Sharps et al., studies on placental morphological changes observed in pregnant women diagnosed with COVID-19 are mainly performed in the third trimester. SARS-CoV-2 was found in 21% of placental samples from COVID-19 cases. Maternal vascular malperfusion (46% of cases), fetal vascular malperfusion (35.3% of cases) and signs of placental inflammation were the most common pathologies of affected placentas. Other placental changes seen in second- and third-trimester placentas include fibrin deposition, infarction, and vascular and intervillous thrombosis. (Sharps et al., 2020) Placental changes are more common in severe cases of COVID-19, but have also been reported in patients with mild form of COVID-19 and even in asymptomatic cases. (Ferraiolo et al., 2020)

In August 2020, a case study of a 26-year-old first-trimester pregnant woman with a live baby and a history of first-trimester miscarriage was published. In the eighth week of pregnancy, she presented with COVID-19 infection. Ultrasound evaluation revealed a fetal death at 13 weeks of gestation (appropriate in size at 10 weeks and 5 days). Virus was detected in first-trimester cytotrophoblast and syncytiotrophoblast 6 weeks after virus was detected in the respiratory tract, although the repeated throat test was negative. The fetus had extensive bilateral pleural effusion and subcutaneous edema, indicating hydrops fetalis. Moreover, SARS-CoV-2 was found in amniotic fluid (by RT-PCR) and fetal membranes (by immunofluorescence of spike proteins). Histopathology of the placenta revealed prominent avascular villi with extensive perivascular fibrin deposition, local syncytiotrophoblast lysis, extensive decidual fibrin deposition, and large, dilated blood vessels. The presence of large numbers of leukocytes, including polymorphonuclear leukocytes, in the decidual bed and intervillous space indicated widespread inflammation. (Shende et al., 2021)

Subsequently, a spontaneous abortion of a twin pregnancy at 13 weeks' gestation in a 28-year-old woman with mild form of COVID-19 was reported. Fetal SARS-CoV-2 infection was confirmed using PCR, immunofluorescence, and viral replication in fetal organs (lungs and kidneys) and placenta, which was consistent with in utero transmission of SARS-CoV-2. (Valdespino-Vázquez et al., 2021)

Therefore, based on data from the current literature, infection with SARS-CoV-2 in the preconception period and in the first half of pregnancy may increase the risk of spontaneous abortion. According to immunopathological mechanisms, reproductive failure is caused by a pro-inflammatory maternal immune response (systemic and/or uterine), thromboembolic events or a direct action of the virus in the uterine environment (endometrium, decidua and trophoblast) (Fig. 1). Moreover, the risk seems to be higher in patients with the severe form of COVID-19, but also in asymptomatic women.

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THE SPECIAL PART

Chapter III. INTRODUCTION

The pandemic infection COVID 19 was born at the beginning of 2020, spreading rapidly in Romania. The number of cases increased, and in a short time the entire medical system went through radical changes, adapting to the new reality. The Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" was no exception, and the measures taken aimed at the safety of the medical staff and the well-being of hospitalized patients and newborn children.

In this sense, with the restructuring and rearrangement of the wards, the testing of all hospitalized patients and the thorough investigation of patients diagnosed with SARS-Cov-2 infection became mandatory. Thus, a routine was created in the performance of blood tests, such as the blood count, coagulation tests, biochemistry and last but not least, the investigation of lung function through X-rays or computer tomography.

Pregnant women have a higher susceptibility to respiratory pathogens due to the anatomical and physiological adaptive changes of the respiratory system that occur during pregnancy, and these viral infections can induce pregnancy complications.

All these data led to the creation of this study, the data of these patients being valuable from the point of view of the knowledge of this new virus, but also of other possible pandemics.

The quality of life of the medical staff has changed considerably in order to continue providing medical services at the highest standards.

It is worth mentioning that during the pandemic, colossal material and medical resources were consumed, which later became a burden for the structures dealing with waste management.

Chapter IV. THE PURPOSE AND OBJECTIVES OF THE RESEARCH

SARS-COV-2 is a new infection with a major impact on the entire world map, quickly becoming one of the pandemics that will mark the history of the world. The data on this virus is still under investigation.

In this study, I propose to illustrate data regarding the real incidence of patients who were diagnosed with COVID-19 during pregnancy and were hospitalized in the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" Braşov.

I also propose to emphasize the main maternal-fetal complications that occurred during the three trimesters of pregnancy and the obstetrical conduct applied in order to solve them as efficiently as possible. At the end, I will compare the obtained results with the data published in the specialized literature up to the present moment.

The aim of this thesis is to develop a management strategy for pregnant women with Sars-Cov-2 infection diagnosed during pregnancy who develop maternal or fetal complications or not. Given that in Romania there is no such elaborate synthesis of obstetric patients, this thesis could serve as a landmark in the creation of a national guide.

The specific objectives of this work are the following:

- Epidemiological data analysis of patients who were diagnosed with Covid-19 infection, maternal demographic factors, socio-economic status, pregnancy and birth management method, severity of the developed form and vertical transmission
- Establishing new optimal management schemes applied during pregnancy that could improve its evolution
- Elaboration of correct obstetric conduct to decrease the number of maternal-fetal complications
- Analysis of epidemiological data through the lens of maternal-fetal complications that occurred during the pandemic
- Establishing potential links between the risk factor of COVID 19 and the multiple complications occurring at various times during pregnancy (trimester I, trimester II, trimester III) and at the time of birth
- Emphasizing some aspects aimed at the quality of life of patients during the pandemic through the lens of measures to combat the SARS-Cov-2 virus
- Analysis of the cost-benefit ratio in the management of pregnant women with SARS-CoV-2 infection
- Highlighting the weight of Sars-Cov-2 infection in the occurrence of feto-maternal complications

Chapter V. RESEARCH MATERIAL AND METHOD

The research was carried out in the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" Brașov. This was based on a prospective study carried out over a period of 2 years and 3 months (01.01.2020-08.03.2022).

The design of the study involved a cohort, longitudinal, prospective research, which included the population of pregnant women hospitalized during the period mentioned above. (Figure V-1)

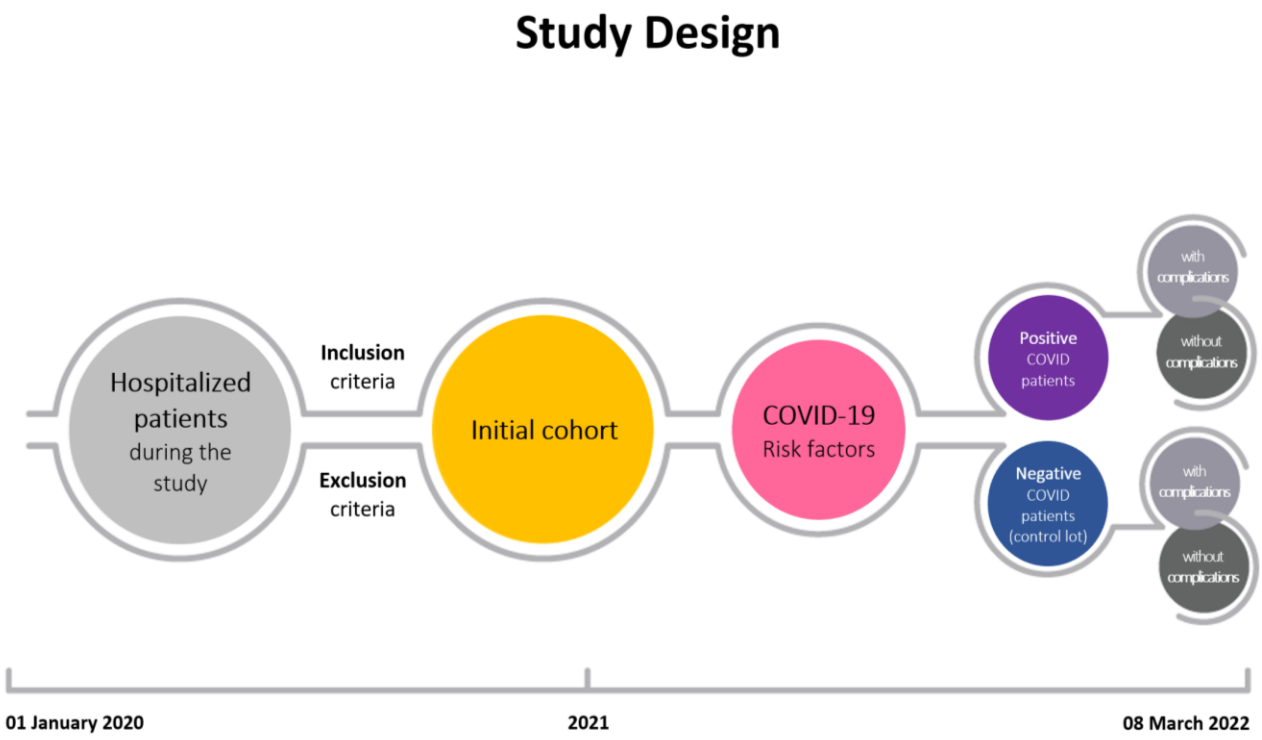
The formation of the initial cohort consisted of the selection of all hospitalized patients between 01.01.2020 and 03.08.2022, regardless of the hospitalization diagnosis. About 10 thousand patients were hospitalized. To create the study group, the following inclusion criteria were applied:

- Pregnant patients in trimester I, II, or III
- Patients transferred from other hospital units diagnosed with SARS-CoV-2 infection
- Patients who are not in evidence with mental illnesses
- Patients who have reached the age of 16
- We used the following exclusion criteria:
- Patients who have not reached the age of 16 at the time of admission
- Patients who are known to have psychiatric diseases.

After passing the patients through these filters, an initial cohort consisting of two groups resulted: a group of patients diagnosed with SARS-CoV-2 infection, numbering 555, and respectively a control group of 287 pregnant women who did not have a positive COVID-19 test at admission or throughout the study period.

Virus detection techniques were used to diagnose patients with COVID 19 infection. The first technique consisted of a rapid test for the qualitative detection of IgG and IgM antibodies to SARS-CoV-2 in human whole blood, serum and plasma samples. (Figure V-1) The second technique carried out consisted in the detection of SARS-CoV-2 Viral RNA through a Real Time - PCR device, which uses a technique to amplify the viral genetic material, being a specific test for detecting the infection.

Figure V-1. Study design



The data necessary for the realization of this thesis were recorded and extracted from the clinical and paraclinical observation sheets of the patients, from the birth registers, from the intensive therapy sheets and from the imaging examination bulletins, to the extent of their inclusion in the present study. The data were analyzed differently for the obtained results, being later compared with the data from the specialized literature. The study thus generated 2 groups of patients, as follows:

- Lot "Exposed" to the risk factor, assumed in the research hypothesis (diagnosed with SARS-CoV-2 infection), represented by pregnant patients, in the I, II, or III trimester of pregnancy, admitted to the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" Brașov
- A control group of patients, "not exposed" to the risk factor assumed in the research hypothesis (who were not diagnosed with SARS-CoV-2 infection), pregnant, in the I, II, or III trimester during the hospitalization.

The effects pursued by the researcher (outcomes) were represented by the appearance in both groups of classic feto-maternal complications as follows:

a. Maternal complications:

- Premature birth
- Premature rupture of membranes
- First trimester spontaneous abortion
- Second trimester spontaneous abortion
- Stopping the pregnancy from progressing
- Threat of abortion
- Coagulation disorders (including DIC)
- Hepatic cytolysis syndrome
- Inflammatory syndrome
- Premature detachment of a normally inserted placenta

b. Fetal complications

- Intrauterine fetal death
- Prematurity
- Acute and chronic fetal distress (ICU)
- SARS-CoV-2 infection

The final results related to the observed effects were quantified at the end of the study and were made concrete by their tabular expression in relation to the studied lots.

From an epidemiological point of view, classical parameters related to risks, such as RR and RA, were calculated. For these, in the statistical analysis compartment, estimates were made using the 95% CI.

The descriptive statistics stage concretized the exposure from an epidemiological point of view of the biological data of the patients, taken from the conditions of birth and from the observation sheets.

Later, for processing, they were entered into a common database, made with the help of the Microsoft Excel program. To create this database, the following biomedical parameters were tracked and recorded for each individual case:

1. data about the mother: mother's age, origin, number of pregnancies and births, gestational age, laboratory analyzes and imaging;
2. data regarding the Covid 19 infection: symptomatology, severity of the disease, treatment, need for admission to the Intensive Care Unit;
3. birth and fetus data: gestational age at which the birth occurred, type of birth, weight of the fetus at birth, Apgar score, infection of the newborn;

V.1.1. Quality of life study in patients with SARS-CoV-2 infection

In order to evaluate the impact of SARS-CoV-2 infection on the quality of life, we created a questionnaire with questions aimed at assessing the general evolution, psycho-emotional damage, the perception of the changes caused by the viral infection, as well as the assessment of intra-hospital measures to combat the transmission of the virus. The questionnaire was sent in digital format to pregnant women who were hospitalized in the Obstetrics and Gynecology Clinical Hospital "Dr. I. A. Sbârcea", Brașov, in the period March 2020 - March 2022, and the results include the answers of the people who responded to the request. The questionnaire was completed by a group of 110 pregnant people.

Table V-1. Questionnaire on the quality of life after SARS-CoV-2 infection

No. Crt.	Questionnaire quality of life after SARS-CoV-2 infection
1	Assess the general condition at the time of discharge by comparison with the time of admission.
2	To what extent did you feel unwell, depressed or hopeless during the hospital stay?
3	Were there symptoms of a psychosomatic nature (eg: insomnia, insecurity, anxiety) during the hospitalization?
4	To what extent have you been emotionally affected by your health problems since SARS-CoV-2 infection was confirmed or symptoms appeared?
7	To what extent have you been emotionally affected by your health problems since SARS-CoV-2 infection was confirmed or symptoms appeared?
6	To what extent did you feel the impact of the lack of visits from loved ones during hospitalization?
5	5 To what extent do you feel your quality of life has been affected post-Covid?
8	To what extent do you consider that the measures taken against the SARS-CoV-2 infection have helped to stop or reduce the transmission of the virus?
9	To what extent do you think patient-staff communication has been affected?

10	To what extent would you propose revisions in the management of stopping the transmission of SARS-COV-2 infection within SCOG-BV?

V.1.2. Graphical data processing and statistical analysis

The statistical and graphic processing of the data used to carry out the prospective study from January 1, 2020 to March 3, 2023 was carried out with the help of Microsoft Excel, GraphPad prism 9.2.0 and GPOwer3.1 programs. The obtained results were rendered as variables. Then correlations were made for the types of variables obtained by analysis using GraphPad prism 9.2.0 and GPOwerWin3. Multivariable analysis for explanatory purposes was carried out with the help of logistic regression or linear regression, in order to find out the role that certain covariates could have on the target effect. Hypotheses with a p value lower than 0.05 were considered statistically significant.

The GraphPad prism 9.2.0 program has the ability to return the correlation coefficient between two variables in the context of a statistical significance level, defined by a p-value 0.9= excellent model, 0.8-0.9= very good model, 0.7-0.8= good model , 0.6-0.7=intermediate model (correct)

V.1.3. Measures provided for compliance with the rules of bioethics and deontology of research

During the prospective study, the norms of bioethics and deontology of scientific research were respected. In the present study we did not use explicit data about patients that could reveal their identity, the number of observation sheets or other personal identification data.

The analysis of the medical documents was carried out with the approval of the Ethics Commission of the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" Braşov.

The patients included in the study signed the informed consent regarding the participation in the medical education and also the informed consent regarding the processing of personal data (GDPR) upon hospitalization.

Chapter VI. RESULT

VI.1.1. Comparative study of the births of patients with and without SARS-CoV-2 infection

Table VI-1. Distribution of births of Covid-negative and Covid-positive patients during 2020-2021

	2020		2021	
Month	Non-Covid	Covid	Non-Covid	Covid
January	372	0	363	28
February	320	0	299	11
March	348	0	369	32
April	380	4	321	26
May	409	7	353	6
June	379	24	347	2
July	344	36	381	0
August	371	13	370	3
September	412	14	397	13
October	367	16	345	55
November	347	49	322	38
December	311	41	367	5

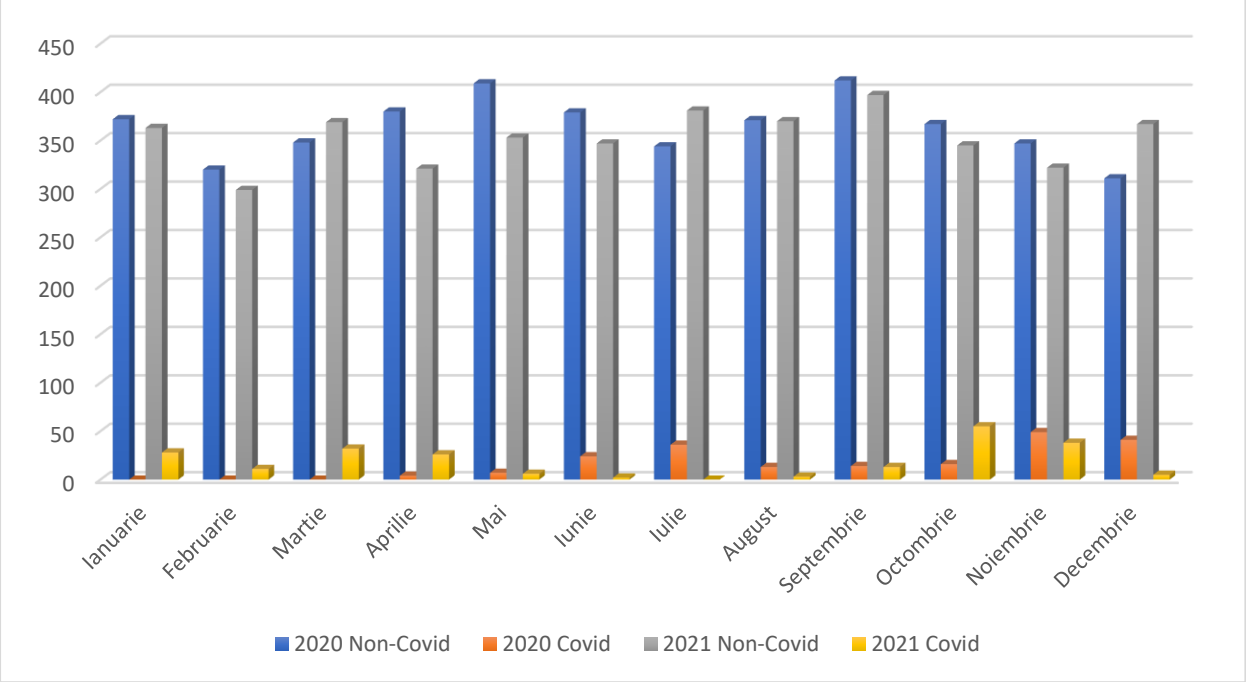


Figure II.12-1. Distribution by month of hospitalized patients according to the presence or absence of SARS-CoV-2 infection

VI.2. Research on the epidemiological data of pregnant patients in the period 2020-2022 within the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea"

VI.2.1. Comparative study of patients with and without SARS-CoV-2 infection depending on the environment of origin

Table VI-2. Distribution of positive COVID patients according to the environment of origin

RURAL	293
URBAN	262

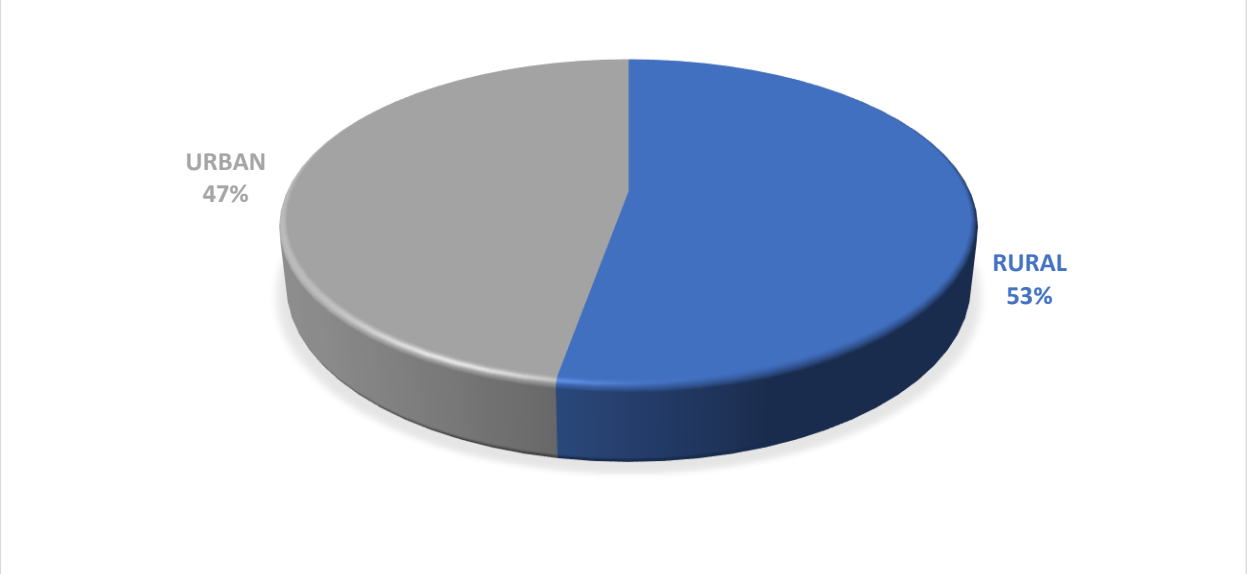


Figure VI.2-1. The structure of the batch of positive COVID patients according to the environment of origin

Table VI-3. Distribution of patients in the control group according to the environment of origin

RURAL	175
URBAN	112

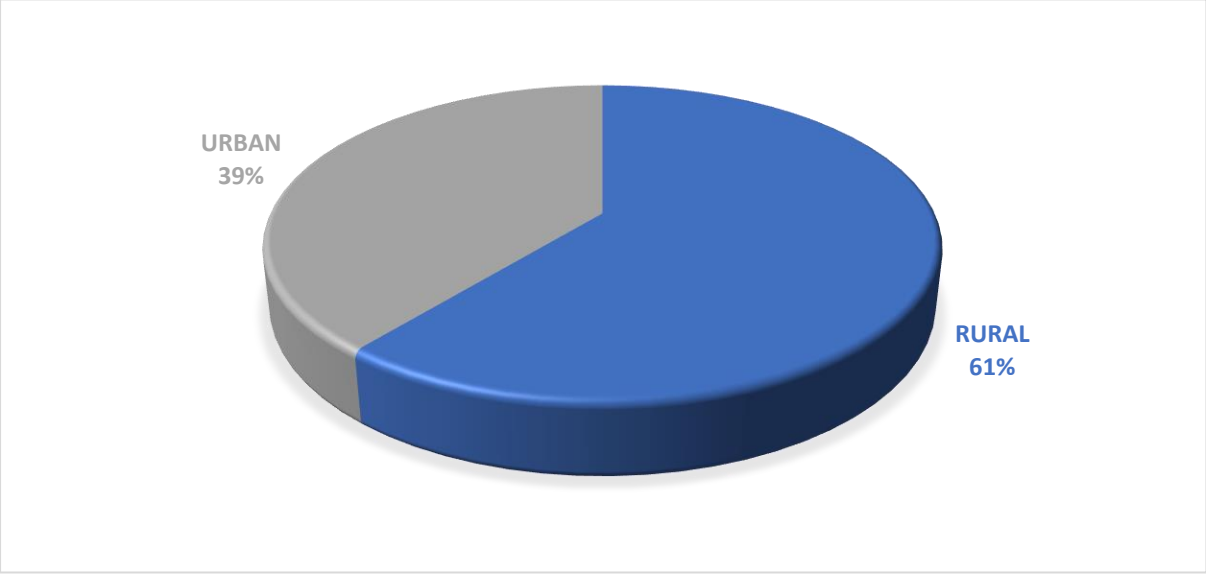


Figure VI.2-2. The structure of the control group according to the environment of origin

Table VI-4. Comparative statistical study of patients with and without SARS-CoV-2 infection depending on the environment of origin

Table Analyzed	**provenientă c vs m**
P value and statistical significance	
Test	Chi-square with Yates' correction
Chi-square, df	4,805, 1
z	2.192
P value	0.0284
P value summary	*
One- or two-sided	Two-sided
Statistically significant (P < 0.05)?	Yes

VI.2.2. Comparative study of patients with and without SARS-CoV-2 infection according to smoker/non-smoker status

Table VI-5. Distribution of positive COVID patients according to smoker/non-smoker status

Smoker	**165**
Non-smoker	341

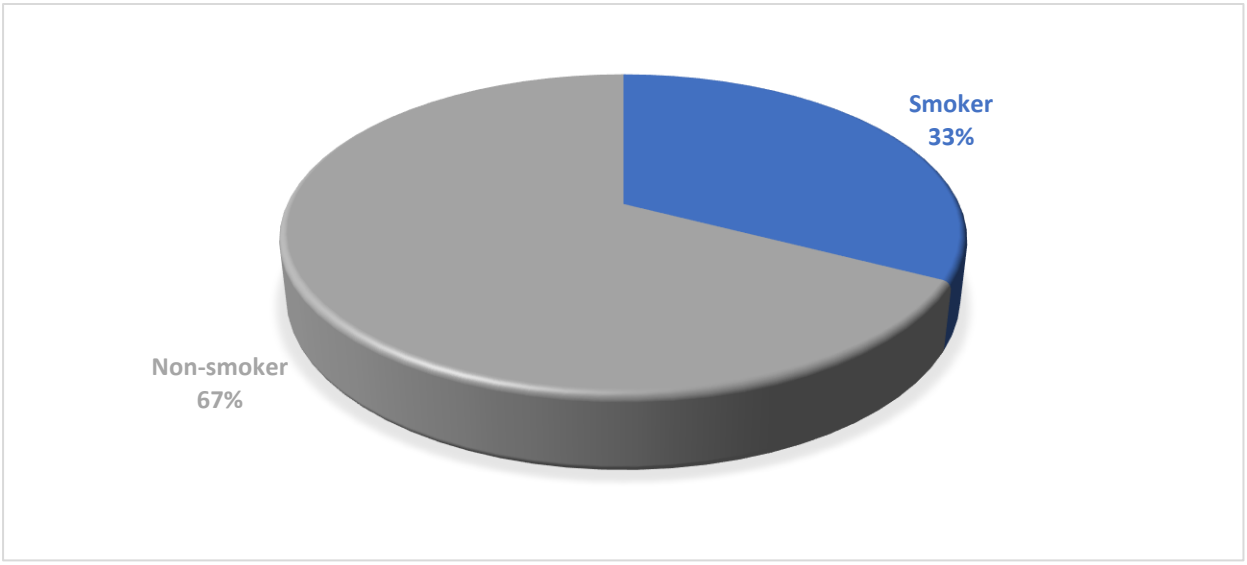


Figure VI.2-3. Group structure of positive COVID patients according to smoker/non-smoker status

Table VI-6. Distribution of negative COVID patients according to smoker/non-smoker status

Smoker	**86**
Non-smoker	197

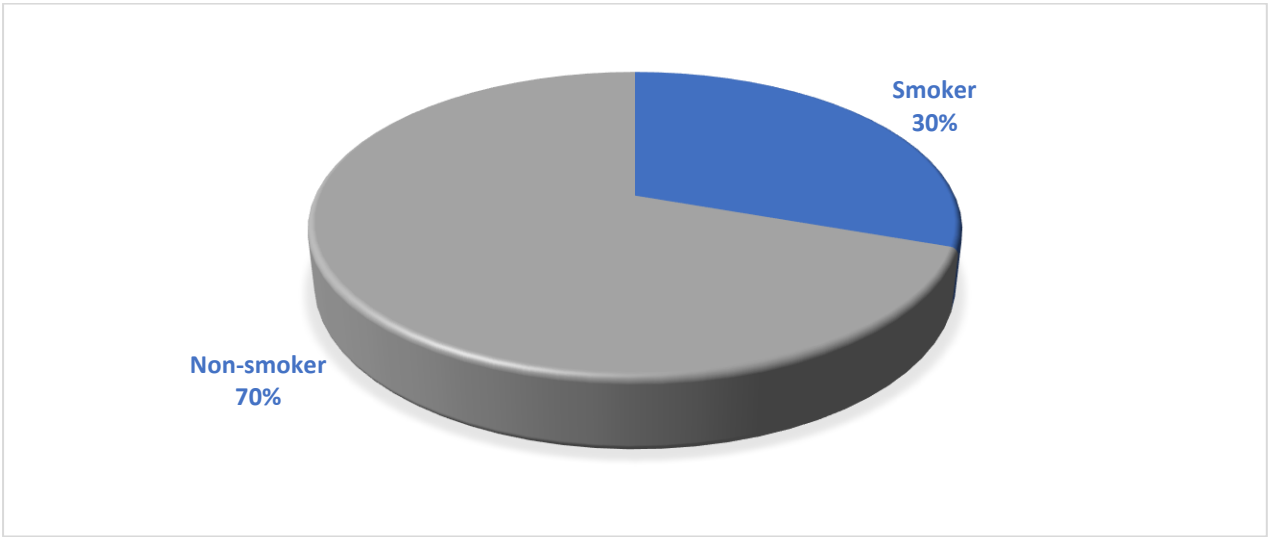


Figure VI.2 8. Group structure of patients without COVID infection according to smoker/non-smoker status

Table VI 14. Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to smoking/non-smoking status

P value and statistical significance	
Test	Fisher's exact test
P value	0.577
P value summary	ns
One- or two-sided	Two-sided
Statistically significant (P < 0.05)?	No

VI.3. Comparative research on the obstetrical data of patients with or without Sars-Cov 2 infection, hospitalized between 01.01.2020-03.08.2022 in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea"

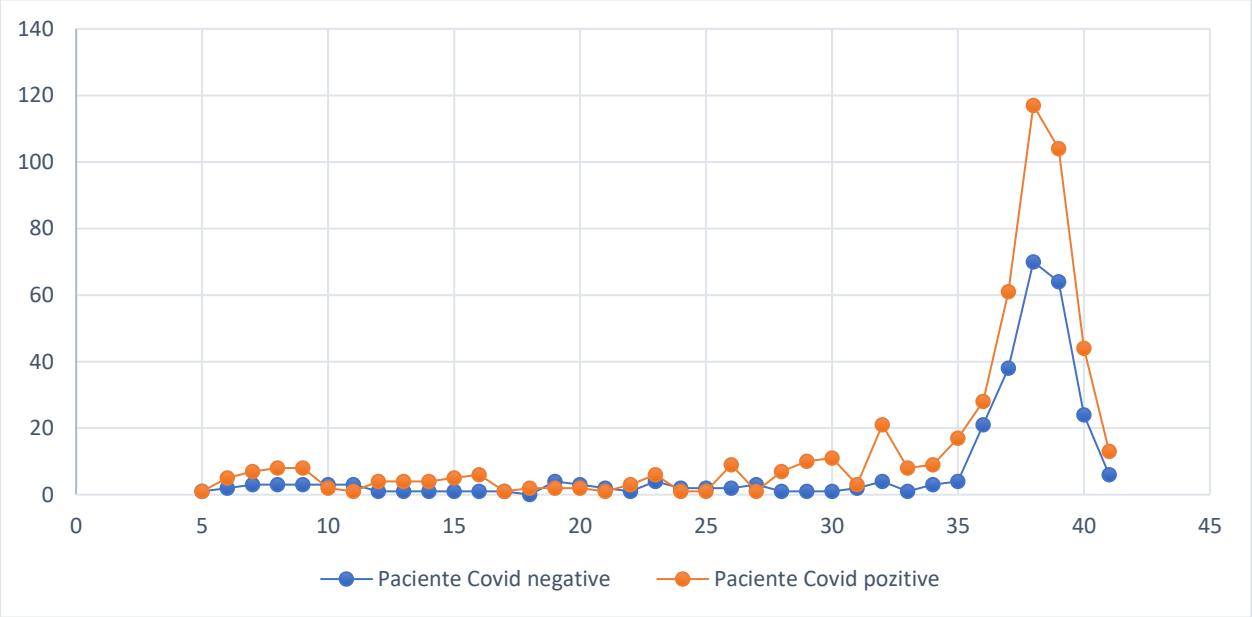


Figure VI.3-1. Comparative analysis of the patients in the study group according to the gestational age at the time of hospitalization

VI.4. Comparative analysis regarding childbirth in patients with or without Sars-Cov 2 infection, hospitalized between 01.01.2020-03.08.2022 in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea"

Table VI-8. Distribution of positive COVID patients according to the type of birth

Spontaneous birth	**181**
Cesarean section	241

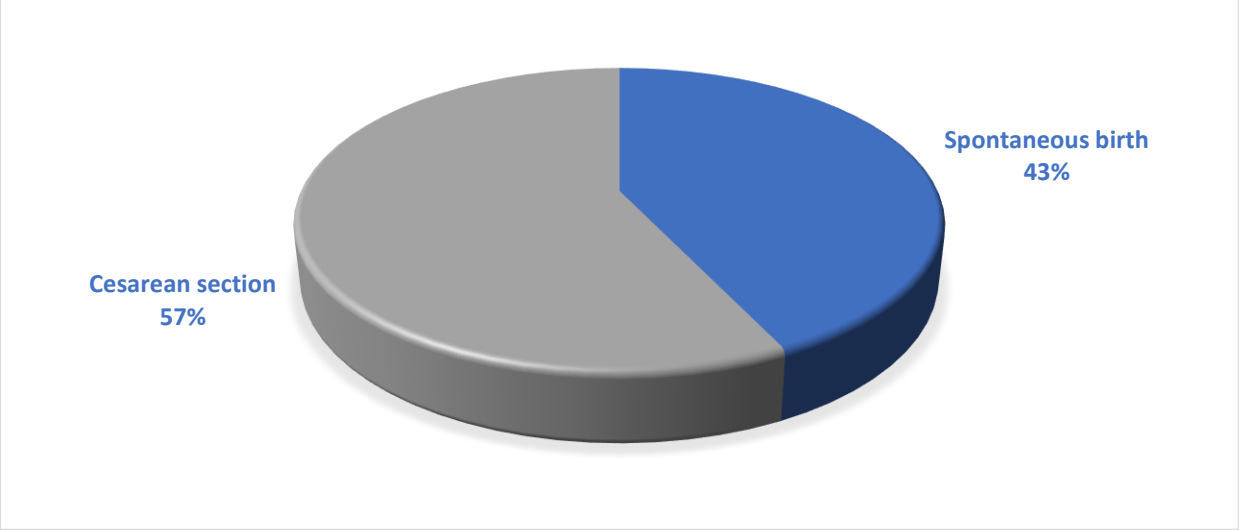


Figure VI.4-1. The return of patients from the study group according to the type of birth

Table VI-9 Distribution of patients from the control group according to the type of birth

Spontaneous birth	**124**
Cesarean section	132

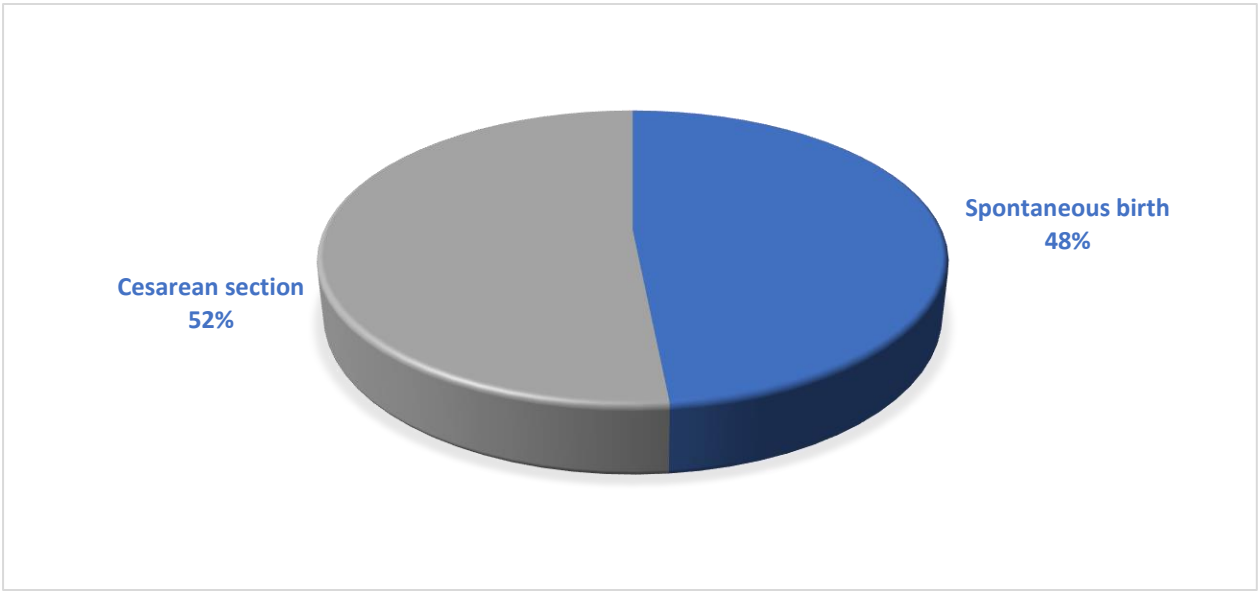


Figure VI.4-2. The return of patients from the control group depending on the type of birth

Table VI-10. Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to the type of birth

P value and statistical significance	
Test	Fisher's exact test
P value	0.1759
P value summary	ns
One- or two-sided	Two-sided
Statistically significant (P < 0.05)?	No

VI.4.1. Comparative study of indications for caesarean section in hospitalized patients with and without SARS-CoV-2 infection

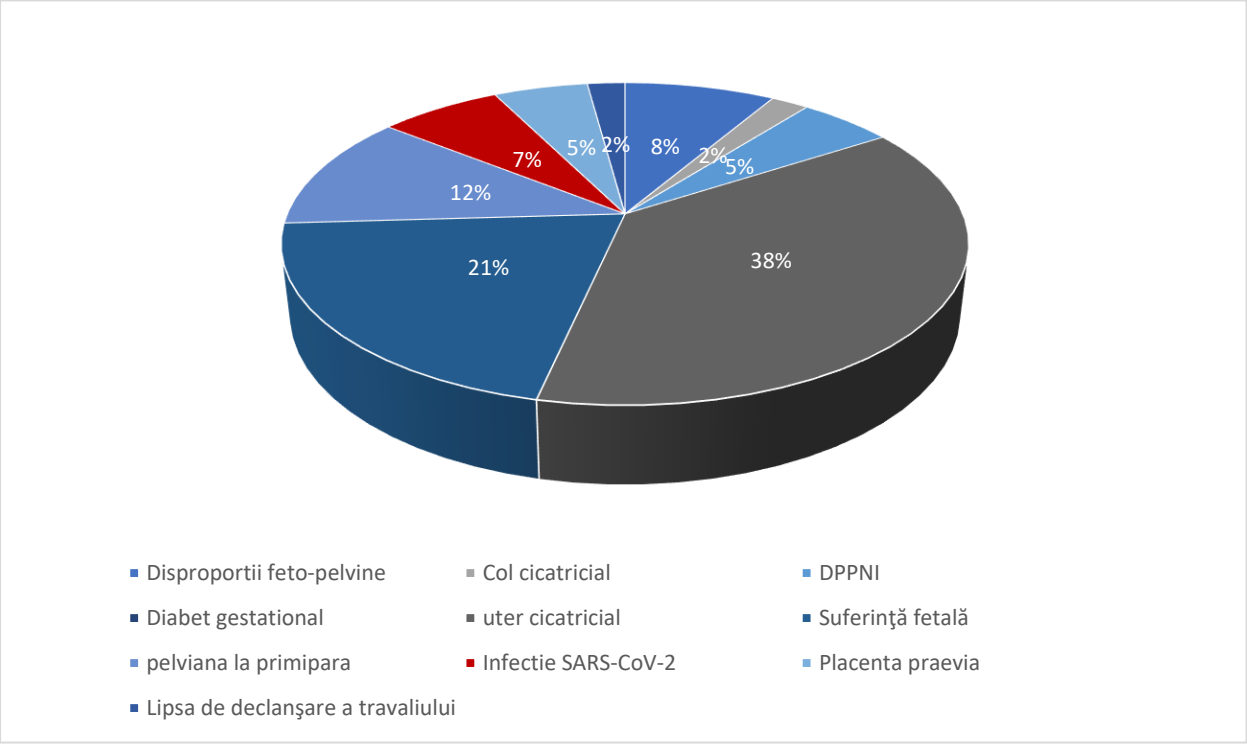


Figure VI.4-3. Distribution of patients with SARS-CoV-2 infection according to the indication for caesarean section

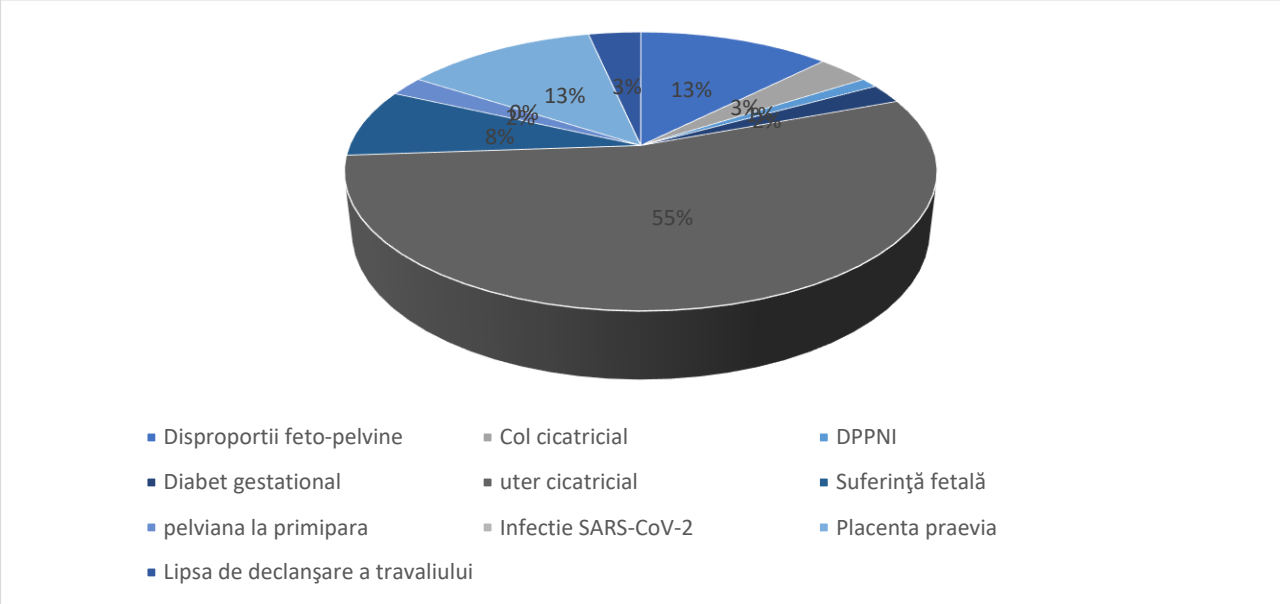


Figure VI.4-4. Distribution of patients without SARS-CoV-2 infection according to the indication for caesarean section

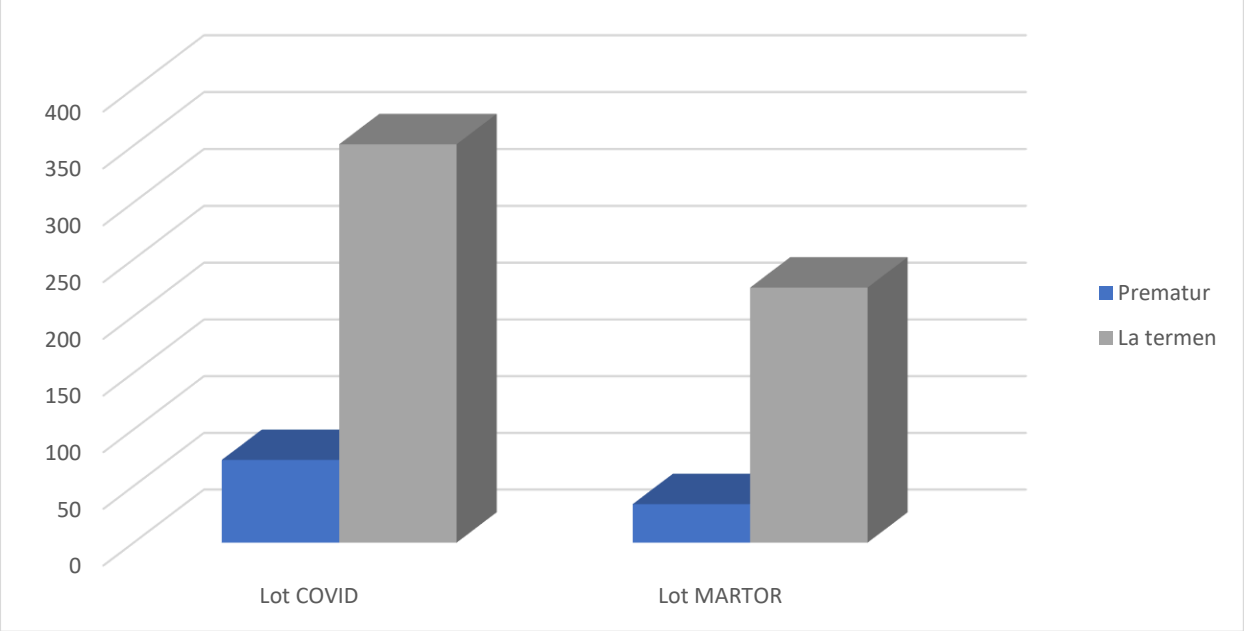


Figure VI.4-5. Comparative analysis of the patients in the study group according to the moment of birth

VI.5. Comparative analysis regarding the condition of newborns in patients with or without Sars-Cov 2 infection, hospitalized between 01.01.2020-03.08.2022 in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea"

VI.5.1. Comparative study of the weight of newborns in hospitalized patients with and without SARS-CoV-2 infection

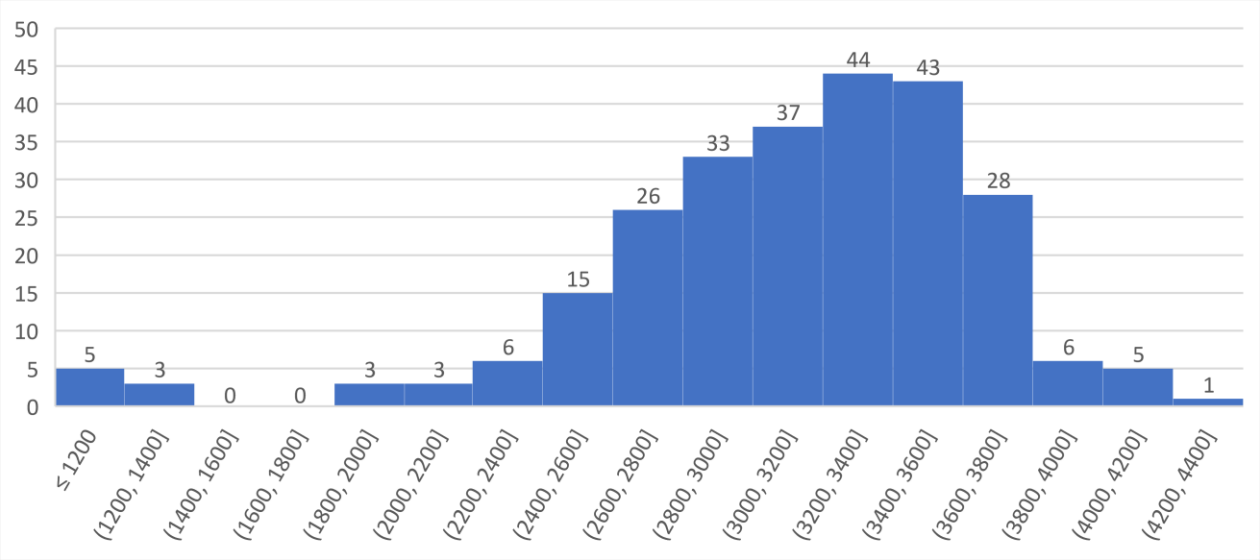


Figure VI.5-1. Histogram representing the birth weight of newborns from the control group

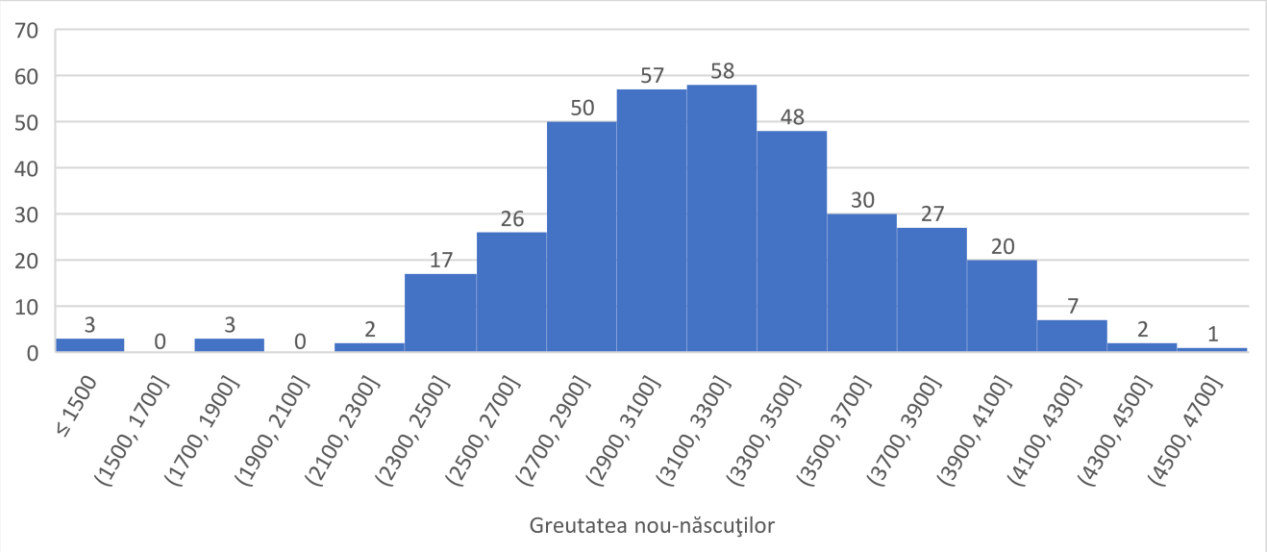


Figure VI.5-2. Histogram representing the birth weight of newborns of patients with SARS-CoV-2 infection

VI.6. Comparative analysis regarding the costs of patients with or without Sars-Cov 2 infection, admitted between 01.01.2020-03.08.2022 in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea"

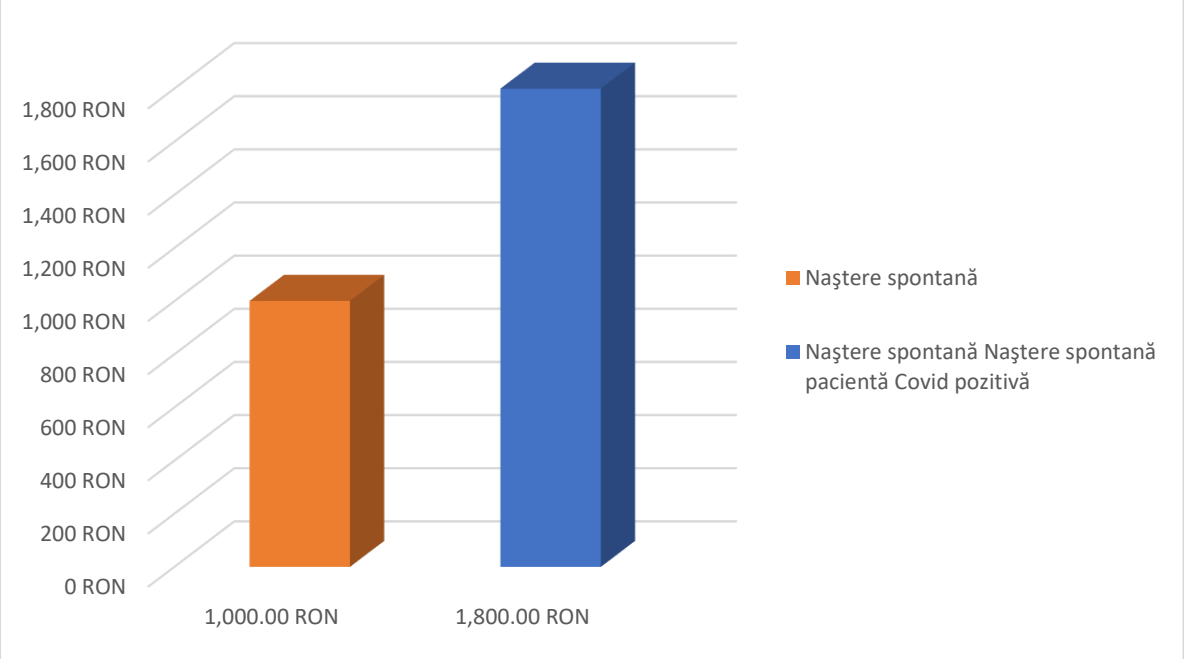


Figure VI.6-1. Comparative graph of the cost of a spontaneous birth in patients with and without SARS-CoV-2 infection

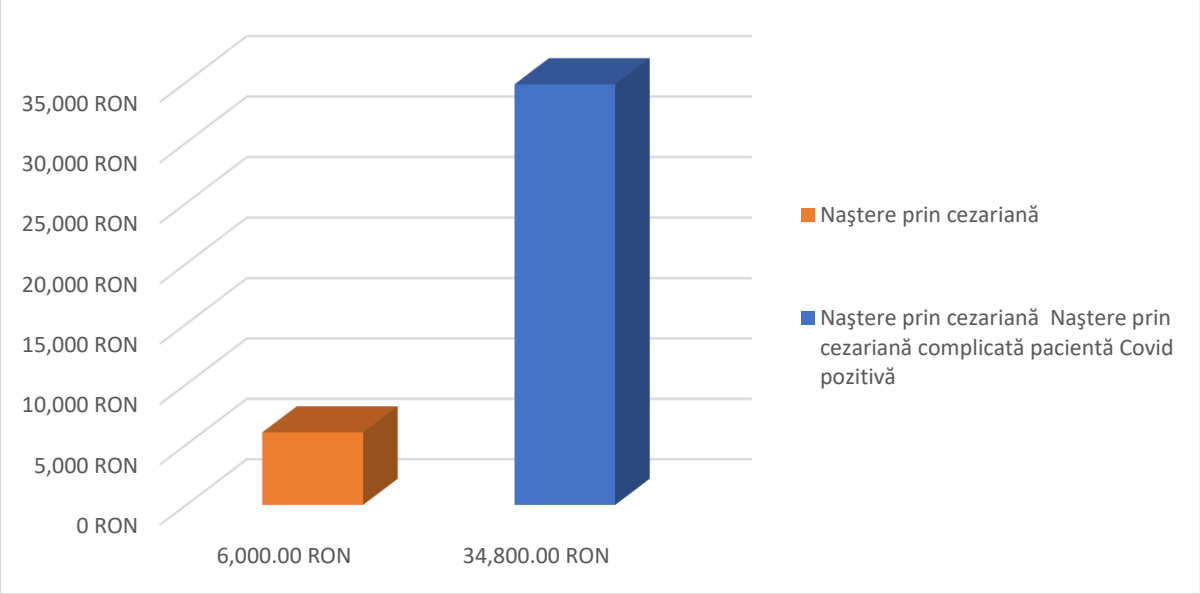


Figure VI.6-2. Comparative graph of the cost of a spontaneous birth in patients with and without SARS-CoV-2 infection

VI.6.1. Comparative study of paraclinical investigations in hospitalized patients with and without SARS-CoV-2 infection

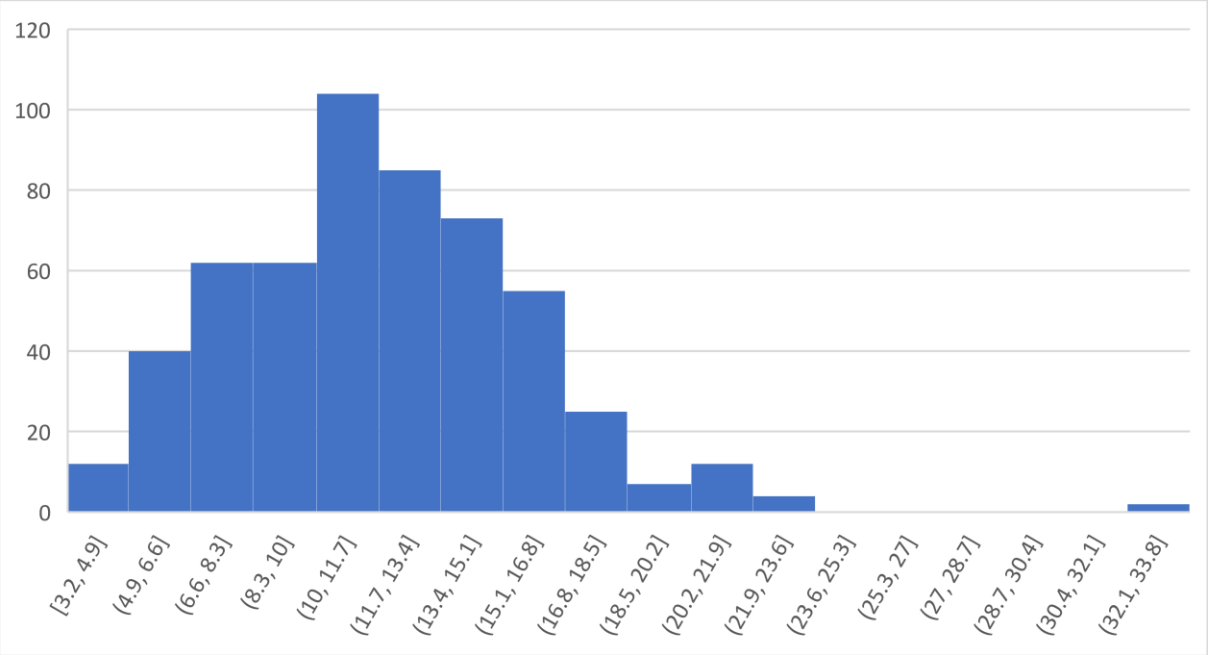


Figure VI.6-3. Histogram representing the number of leukocytes in patients with SARS-CoV-2 infection (10*9/l)

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VI.7. Comparative statistical analysis regarding maternal complications in patients with or without Sars-Cov 2 infection, hospitalized between 01.01.2020-03.08.2022 within Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea

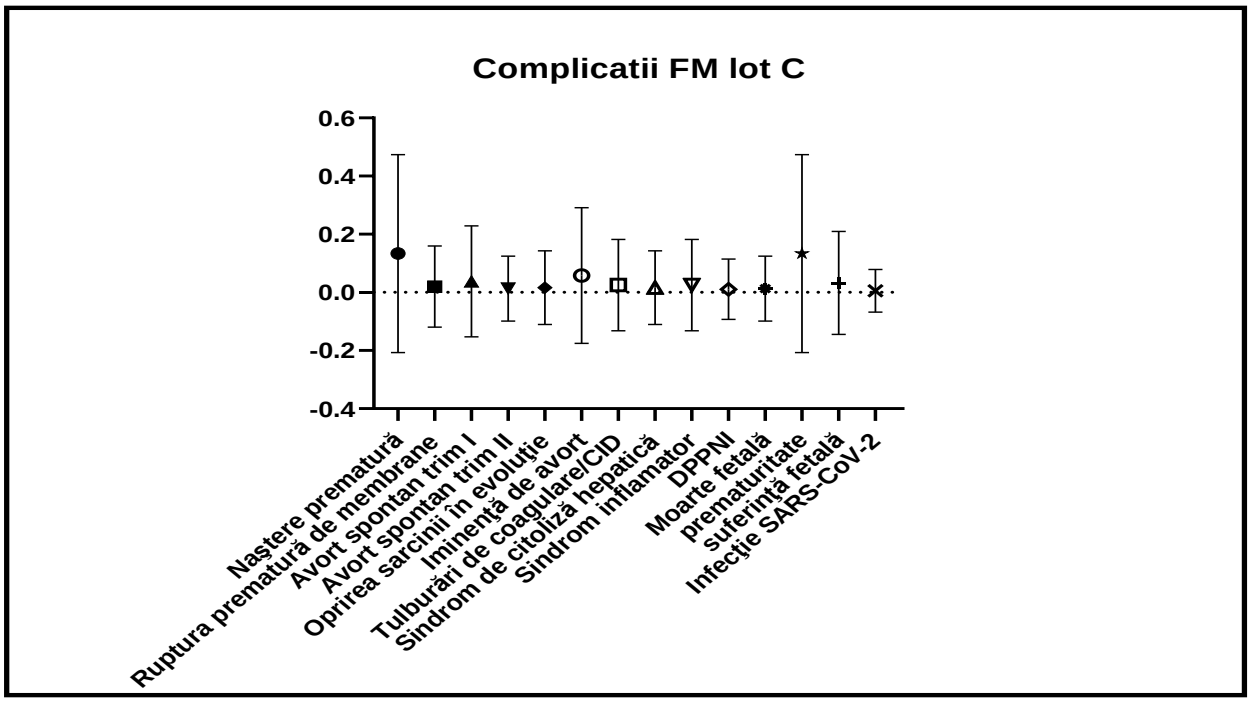

Figure VI.7-1. Statistical analysis of maternal-fetal complications studied within the cohortpatients with SARS-CoV-2 infection

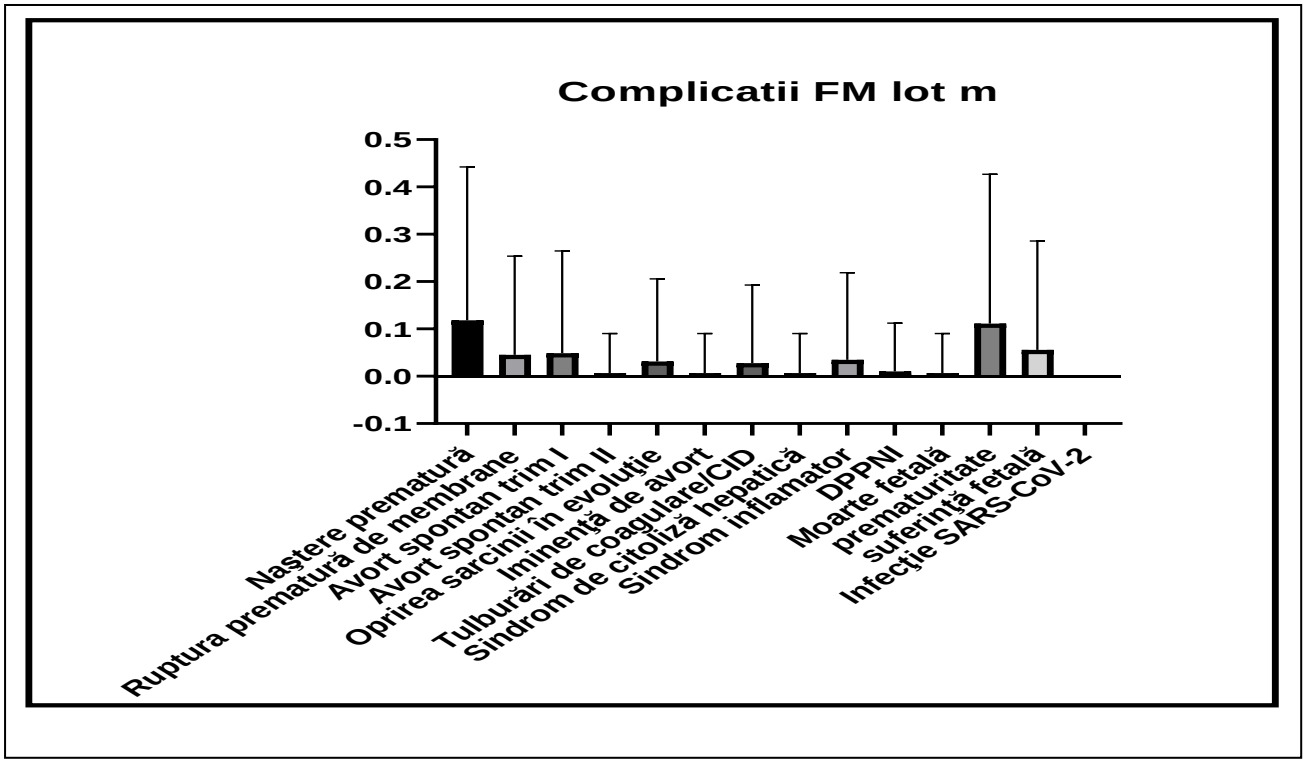

Figure VI.7-2. Statistical analysis of maternal-fetal complications studied in the control group

VI.7.1. Studiu statistic comparativ al naşterii premature la pacientele internate cu şi fără infecție SARS-CoV-2

Tabel VI-11. Distribuția pacientelor din lotul de studiu în fucție de tipul naşterii, prematură sau la termen

	Naştere prematură	**Naştere la termen**
Witness Lot	11,85%	88,15%
Lot of Covid	13,33%	86,67%

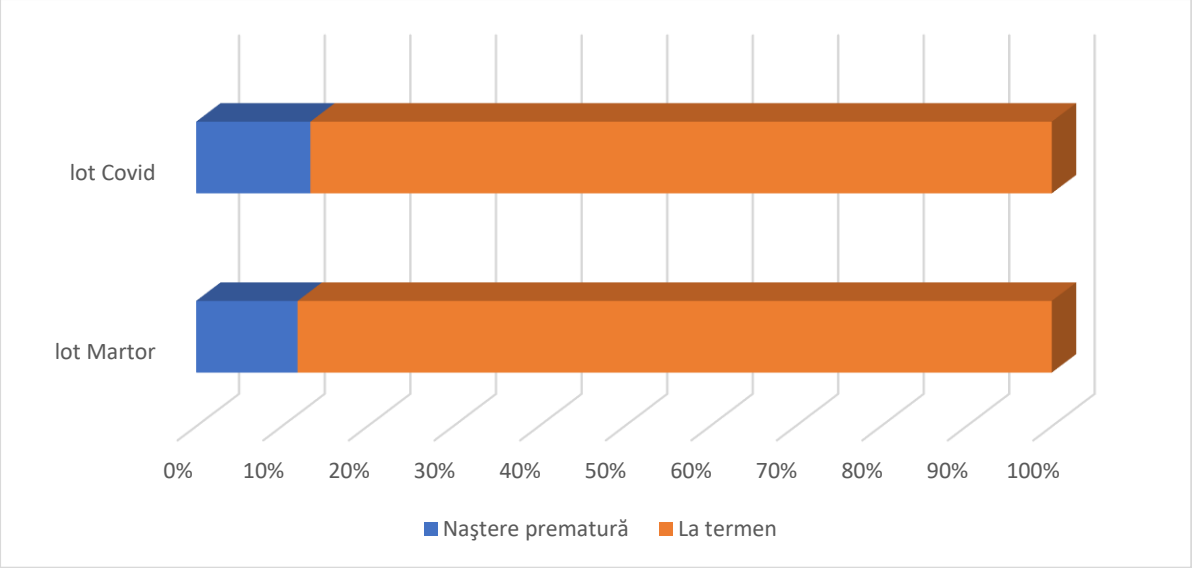

Figure VI.7-3. The structure of the study group according to the type of birth, premature or full-term

Table VI-12. Comparative statistical analysis of patients with and without SARS-CoV-2 infection depending on the moment of birth

Table Analyzed	**Naştere prematură RR**	
P value and statistical significance		
Test	Fisher's exact test	
P value	0.5876	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI

Relative Risk	0.8885	0,6068 to 1,292
Reciprocal of relative risk	1.125	0,7739 to 1,648
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.7.2. Comparative statistical study of patients according to the time of membrane rupture, with and without SARS-CoV-2 infection

Table VI-13. The distribution of patients in the study group according to the time of limb breakage

	Membrane rupte prematur	**Fără membrane rupte prematur**
Lot Martor	13	274
Lot Covid	11	544

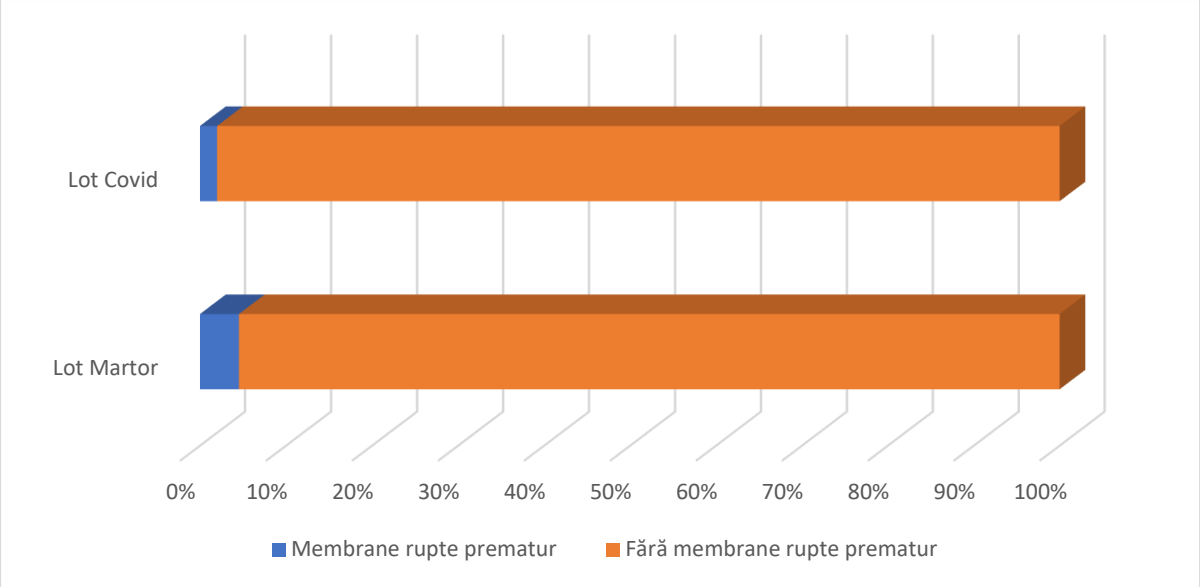

Figure VI 1. The structure of the study group according to the moment of rupture of the membranes

Table VI-14. Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to the time of membrane rupture

Table Analyzed	**Ruptura prematură de membrane**
P value and statistical significance	
Test	Fisher's exact test
P value	0.0476
P value summary	*
One- or two-sided	Two-sided
Statistically significant (P < 0.05)?	Yes

Effect size	Value 95% CI	
Relative Risk	2.285	1,056 to 4,936
Reciprocal of relative risk	0.4376	0,2026 to 0,9469
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.7.3. Comparative statistical study of patients who suffered a spontaneous abortion in the first trimester, with and without SARS-CoV-2 infection

Table VI-15. Distribution of patients in the study groups according to spontaneous abortion

	Avort spontan	**Fără Avort spontan**
Lot Martor	14	273
Lot Covid	21	534

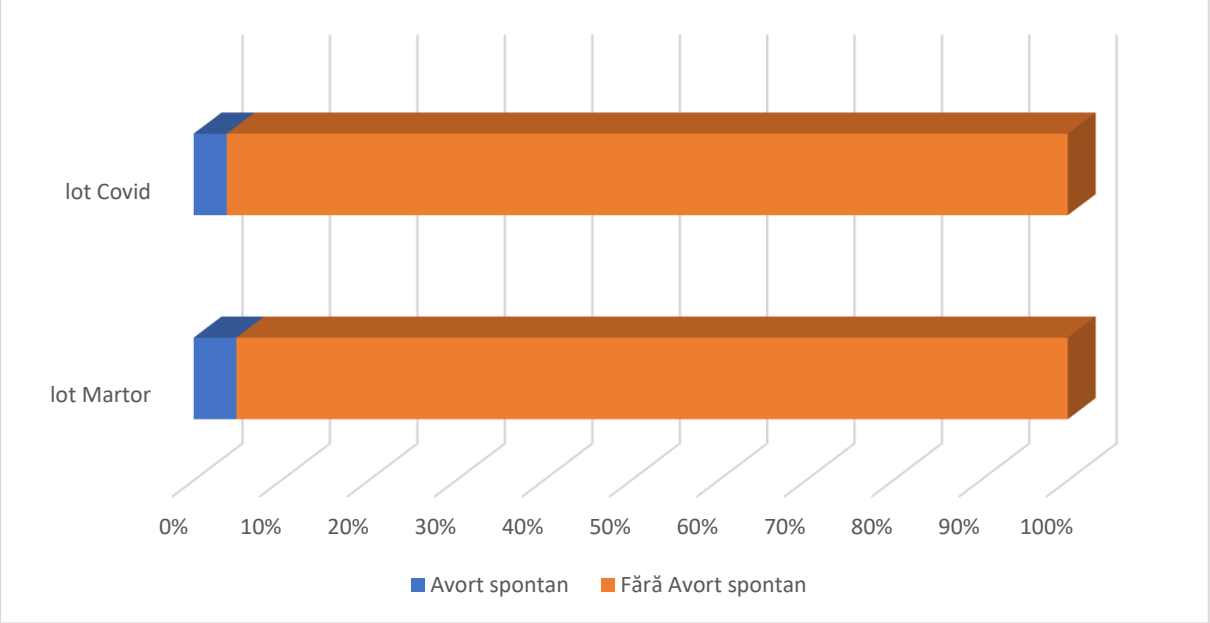

Figure VI-2. Structure of the study group according to the presence of spontaneous abortion in the first trimester

Table VI-16. Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to the presence of first-trimester abortion

Table Analyzed	**Avort spontan trim. I**	
P value and statistical significance		
Test	Fisher's exact test	
P value	0.4691	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI

Relative Risk	1.289	0,6718 to 2,463
Reciprocal of relative risk	0.7757	0,4061 to 1,489
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.7.4. Comparative statistical study of hospitalized patients with threatened abortion with and without SARS-CoV-2 infection

Table VI-17. Distribution of study groups according to the presence of threatened abortion

	Abortion Spontaneous trimester. II	**Without Abortion Spontaneous trimester.II**
Witness Lot	2	285
Covid Lot	7	548

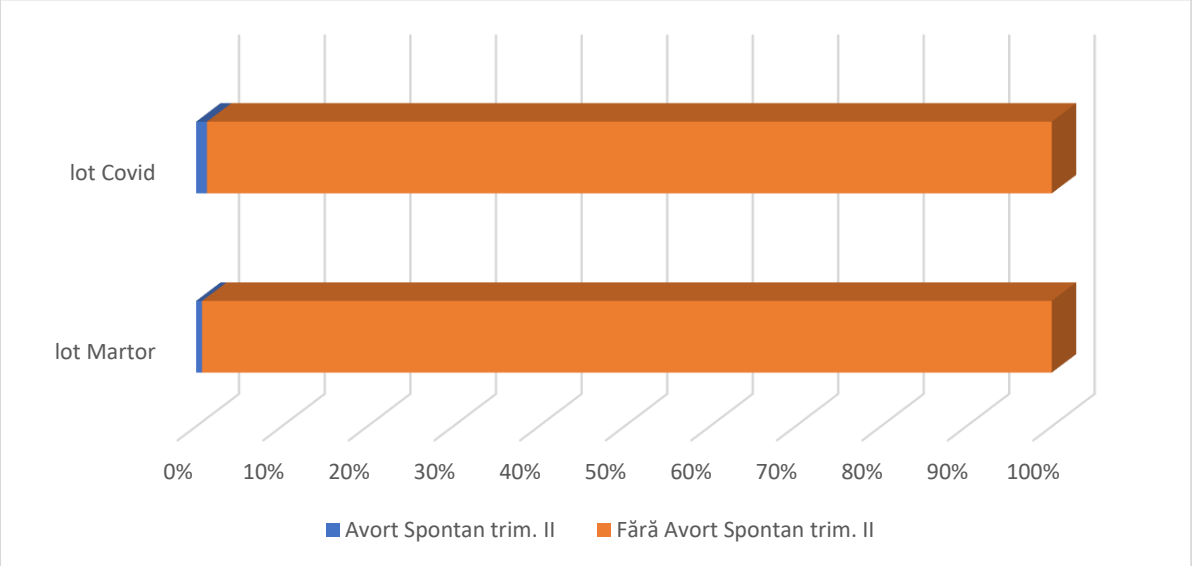

Figure VI-3. Distribution of study groups according to the presence of threatened abortion

Table VI-18. Comparative statistical analysis of patients in the study groups according to the threat of abortion

Table Analyzed	**Avort spontan trim II**	
P value and statistical significance		
Test	Fisher's exact test	
P value	0.7257	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI
Relative Risk	0.5525	0,1309 to 2,317
Reciprocal of relative risk	1.81	0,4315 to 7,639
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.7.5. Comparative statistical study of hospitalized patients according to the occurrence of coagulation disorders

Table VI-19. Distribution of study groups according to the presence of coagulation disorders

	Cu tulburări de coagulare	Fără tulburări de coagulare
Lot Martor	8	279
Lot Covid	14	541

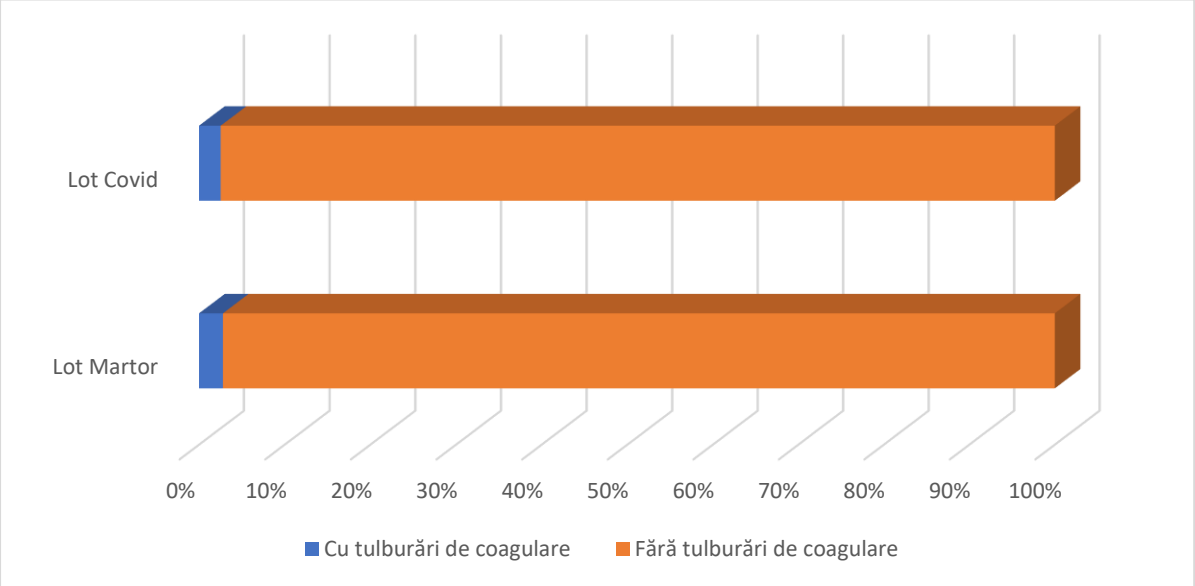

Figure VI-4. The structure of the study groups according to the presence of coagulation disorders

Table VI-20 Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to the occurrence of coagulation disorders

Table Analyzed	**Tulburări de coagulare**	
P value and statistical significance		
Test	Fisher's exact test	
P value	0.8223	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI
Relative Risk	1.105	0,4795 to 2,534
Reciprocal of relative risk	0.905	0,3947 to 2,086
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.8. Comparative statistical analysis regarding fetal complications occurring in the faces of patients with or without Sars-Cov 2 infection, admitted between 01.01.2020-03.08.2022 in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea"

VI.8.1. Comparative statistical study of hospitalized patients with and without SARS-CoV-2 infection, according to fetal death

Table VI-21. Distribution of study groups according to the occurrence of fetal death

	Moarte fetală	Fără moarte fetală
Lot Martor	2	285
Lot Covid	7	548

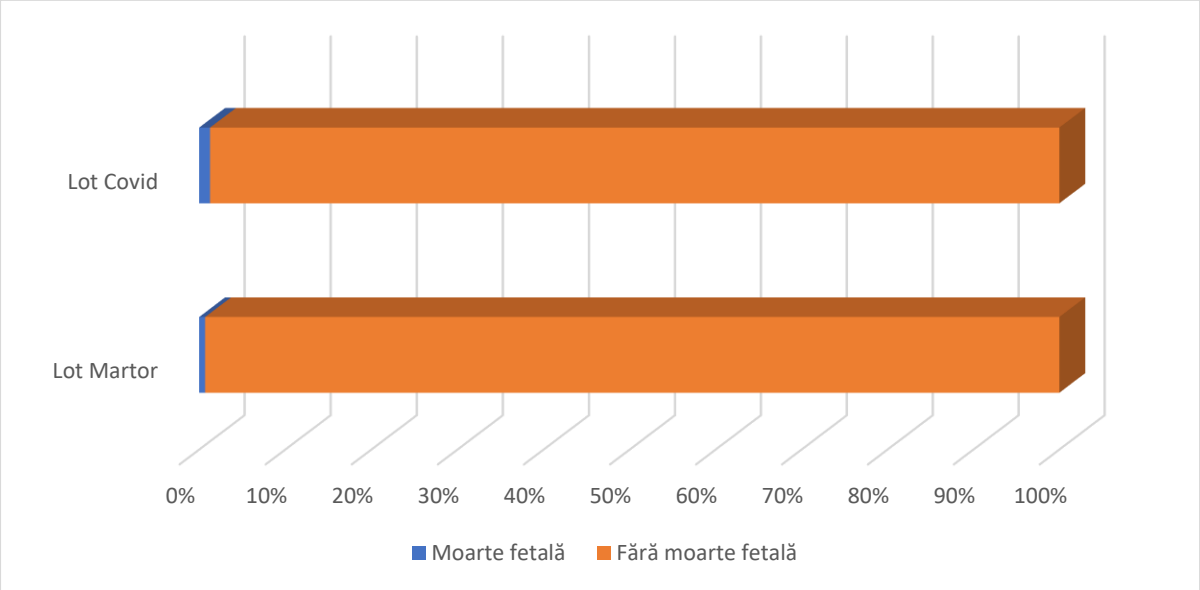

Figure VI-5. Structure of the study groups according to the occurrence of fetal death

Table VI-22. Comparative statistical analysis of patients with and without SARS-CoV-2 infection according to the occurrence of fetal death

Table Analyzed	**Moarte fetală**	
P value and statistical significance		
Test	Fisher's exact test	
P value	0.7257	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI
Relative Risk	0.5525	0,1309 to 2,317
Reciprocal of relative risk	1.81	0,4315 to 7,639
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.8.2. Comparative statistical study of newborns of hospitalized patients with and without SARS-CoV-2 infection, depending on the moment of birth

Table VI-23. Distribution of newborn patients in the study groups according to the time of birth

	Prematuri	**La termen**
Lot Martor	32	255
Lot Covid	74	481

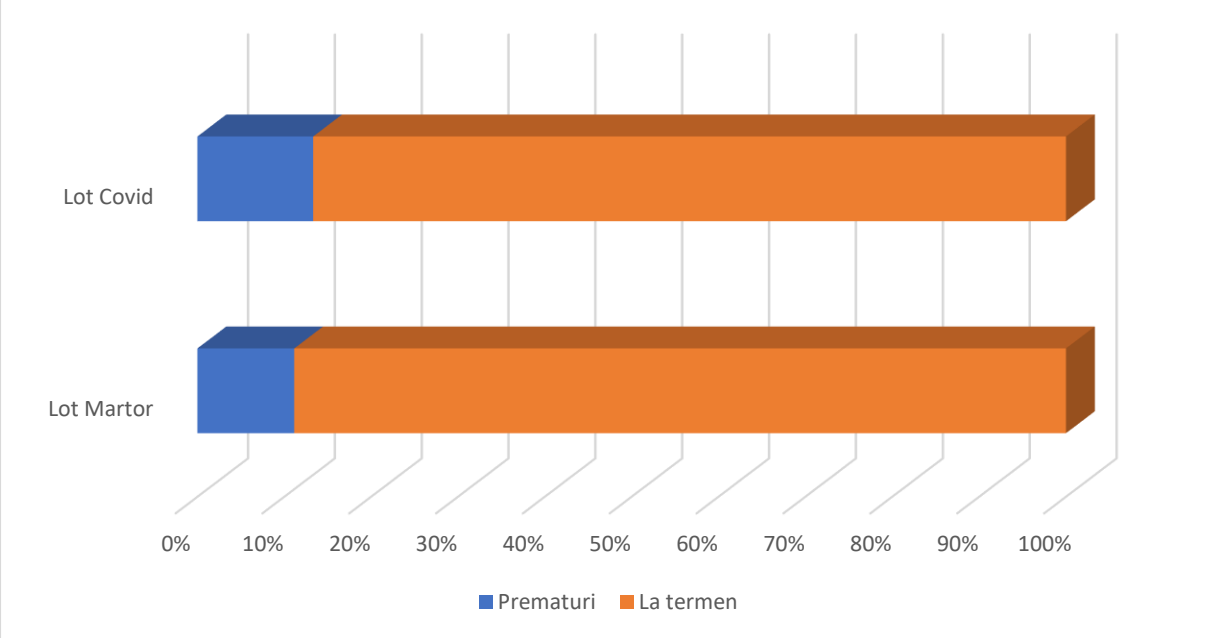

Figure VI-6. The structure of the newborn patients in the study groups according to the time of birth

Table VI-24. Comparative statistical analysis of newborns of patients with and without SARS-CoV-2 infection according to the time of birth

Table Analyzed	**Prematuritate**
P value and statistical significance	
Test	Fisher's exact test

P value	0.383	
P value summary	ns	
One- or two-sided	Two-sided	
Statistically significant (P < 0.05)?	No	
Effect size	Value	95% CI
Relative Risk	0.8362	0,5660 to 1,227
Reciprocal of relative risk	1.196	0,8151 to 1,767
Methods used to compute CIs		
Relative Risk	Koopman asymptotic score	

VI.9. Explanatory multivariable regression regarding the weight of various causal factors (including SARS-CoV-2 infection) in the occurrence of maternal-fetal complications in the studied group

VI.9.1. Explanatory multivariable regression regarding the weight of different causal factors in the occurrence of premature birth

Table VI-25. Explicative multivariable regression regarding the weight of causal factors in the occurrence of premature birth

Analysis of Variance	SS	DF	MS	F (DFn, DFd)	P value
D1 Vârsta sub 19	0.01808	1	0.01808	F (1, 664) = 0,2021	P=0,6532
D2 Vârsta peste 35	0.01123	1	0.01123	F (1, 664) = 0,1255	P=0,7233

Paritate	0.01632	1	0.01632	F (1, 664) = 0,1825	P=0,6694
D1 Comorbidități obstetricale	0.1022	1	0.1022	F (1, 664) = 1,143	P=0,2855
D2 Comorbidități cardiovasculare	0.2439	1	0.2439	F (1, 664) = 2,727	P=0,0991
D3 Comorbidități infecțioase	0.1351	1	0.1351	F (1, 664) = 1,511	P=0,2195
D4 Comorbidități metabolice	0.2353	1	0.2353	F (1, 664) = 2,631	P=0,1053
Greutate fat (1> 2500g,0 <2500 g)	28.75	1	28.75	F (1, 664) = 321,4	P<0,0001
Tipul nașterii	0.2125	1	0.2125	F (1, 664) = 2,376	P=0,1237
Fumatoare (da/nu)	0.02783	1	0.02783	F (1, 664) = 0,3112	P=0,5771
Prezența COVID	0.004538	1	0.004538	F (1, 664) = 0,05073	P=0,8219
Residual	59.39	664	0.08945		
Total	90.06	675			

Table VI-26. Estimated β parameters related to the weight of causal factors in the occurrence of preterm birth

Parameter estimates	**Variable**	**Estimate**	**Standard error**	**95% CI (asymptotic)**	**|t|**	**P value**	**P value summary**
	Intercept	0.6326	0.04273	0,5487 to 0,7165	14.8	<0,0001	****
β1	D1 Vârsta sub 19	-0.01653	0.03677	-0,08873 to 0,05567	0.4496	0.6532	ns

β2	D2 Vârsta peste 35	0.0121	0.03416	-0,05497 to 0,07917	0.3543	0.7233	ns
β3	Paritate	0.01079	0.02526	-0,03881 to 0,06039	0.4272	0.6694	ns
β4	D1 Comorbidități obstetricale	-0.03556	0.03327	-0,1009 to 0,02976	1.069	0.2855	ns
β5	D2 Comorbidități cardiovasculare	0.07456	0.04515	-0,01409 to 0,1632	1.651	0.0991	ns
β6	D3 Comorbidități infecțioase	0.08289	0.06744	-0,04953 to 0,2153	1.229	0.2195	ns
β7	D4 Comorbidități metabolice	0.1328	0.08185	-0,02795 to 0,2935	1.622	0.1053	ns
β8	Greutate fat (1> 2500g,0 <2500 g)	-0.5877	0.03278	-0,6521 to -0,5234	17.93	<0,0001	****
β9	Tipul nașterii	0.04533	0.02941	-0,01242 to 0,1031	1.541	0.1237	ns
β10	Fumatoare (da/nu)	-0.01387	0.02487	-0,06270 to 0,03495	0.5578	0.5771	ns
β11	Prezența COVID	0.005529	0.02455	-0,04267 to 0,05373	0.2252	0.8219	ns

Table VI-27. Determination of multicollinearity regarding the weight of causal factors in the occurrence of preterm birth

Multicollinearity	**Variable**	**VIF**	**R2 with other variables**	
β0	Intercept			

β1	D1 Vârsta sub 19	1.066	0.06211	
β2	D2 Vârsta peste 35	1.065	0.06106	
β3	Paritate	1.178	0.1512	
β4	D1 Comorbidități obstetricale	1.668	0.4005	
β5	D2 Comorbidități cardiovasculare	1.132	0.1169	
β6	D3 Comorbidități infecțioase	1.035	0.03358	
β7	D4 Comorbidități metabolice	1.027	0.0261	
β8	Greutate fat (1> 2500g,0 <2500 g)	1.024	0.02334	
β9	Tipul nașterii	1.619	0.3824	
β10	Fumatoare (da/nu)	1.038	0.03627	
β11	Prezența COVID	1.075	0.06959	
Normality of Residuals	Statistics	P value	Passed normality test (alpha=0,05)?	P value summary
Anderson-Darling (A2*)	93.06	<0,0001	No	****
D'Agostino-Pearson omnibus (K2)	191.1	<0,0001	No	****

Shapiro-Wilk (W)	0.7009	<0,0001	No	****
Kolmogorov-Smirnov (distance)	0.3582	<0,0001	No	****

VI.10. Evaluation of the quality of life after SARS-CoV-2 infection of pregnant women admitted to the "Dr.I.A.Sbârcea" Obstetrics-Gynecology Clinical Hospital during the study period

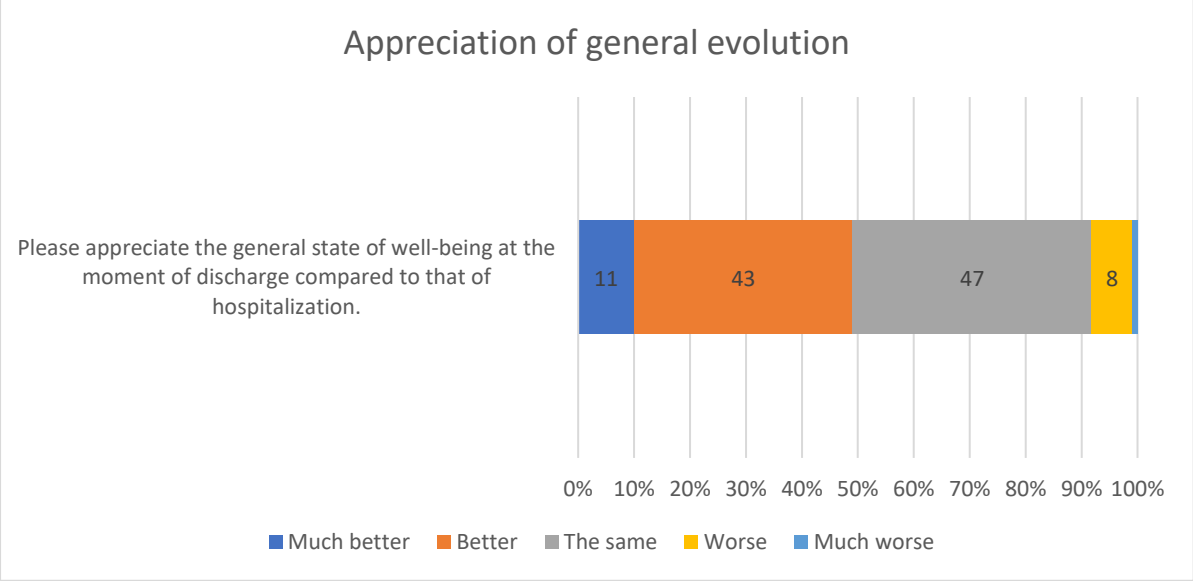

Figure VI-7. The structure of the study group according to the assessment of the general evolution during hospitalization

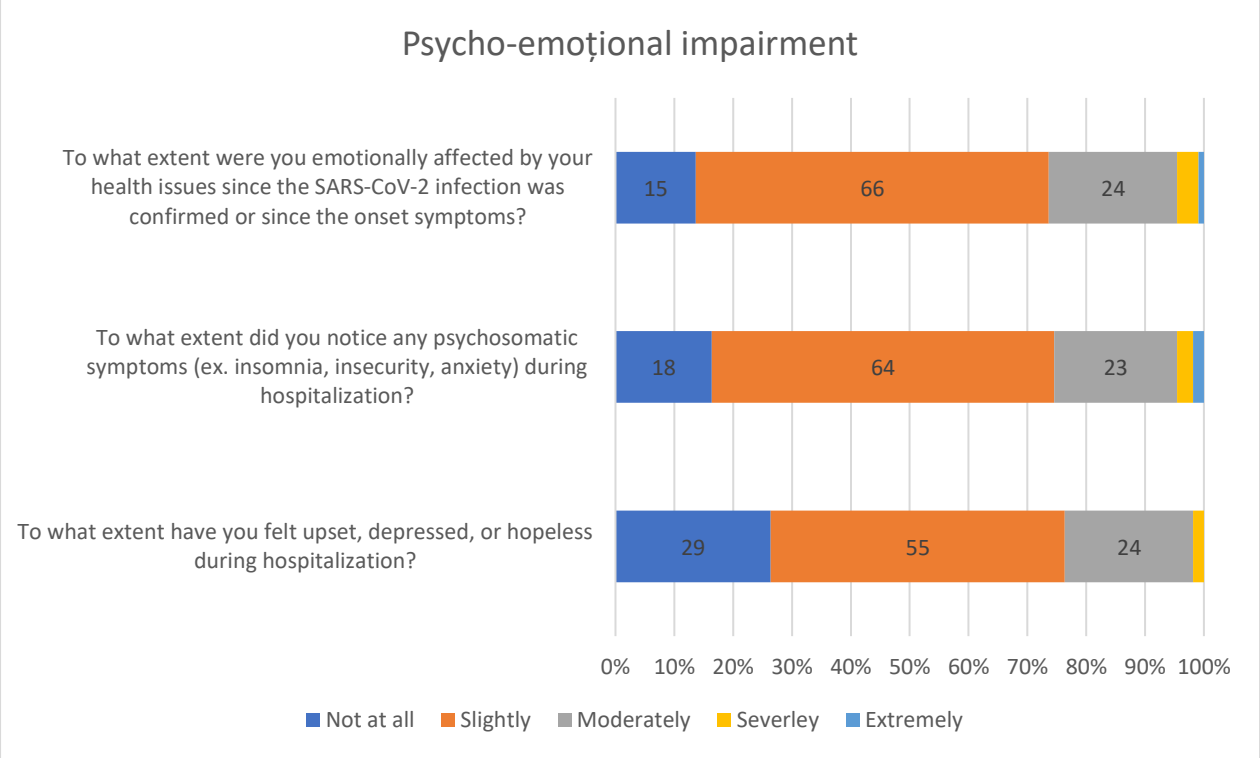

Figure VI-8. The structure of the study group according to the assessment of psycho-emotional impairment

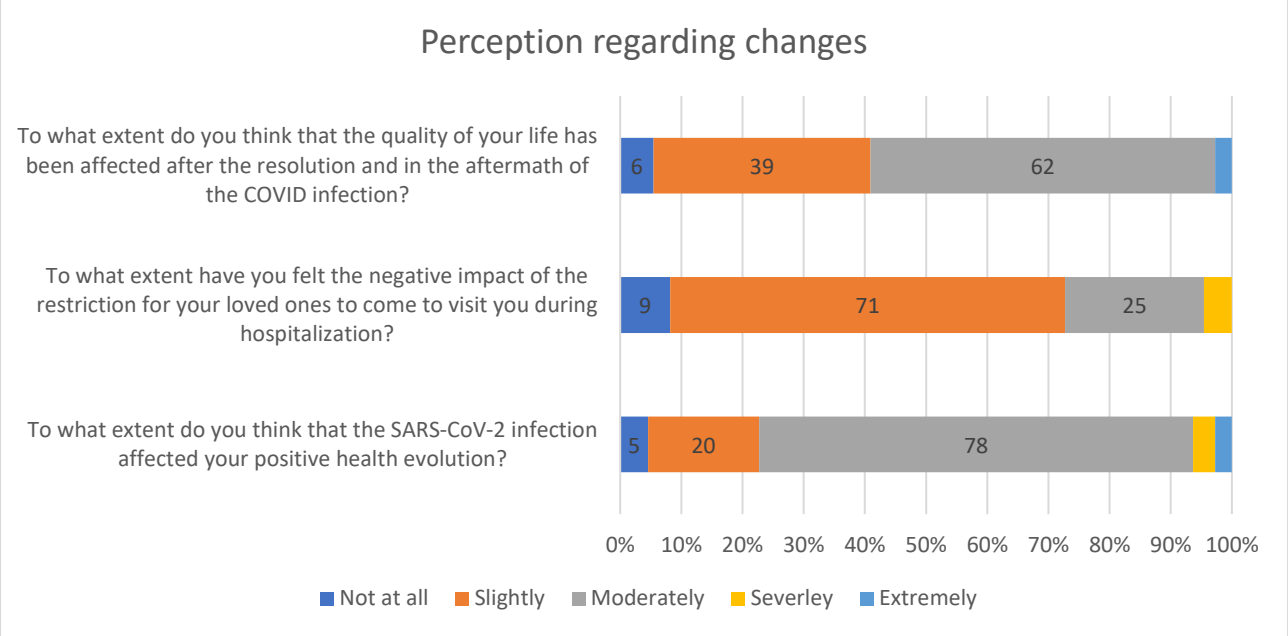

Figure VI-9. The structure of the study group according to the assessment of the perception of the change in the quality of life

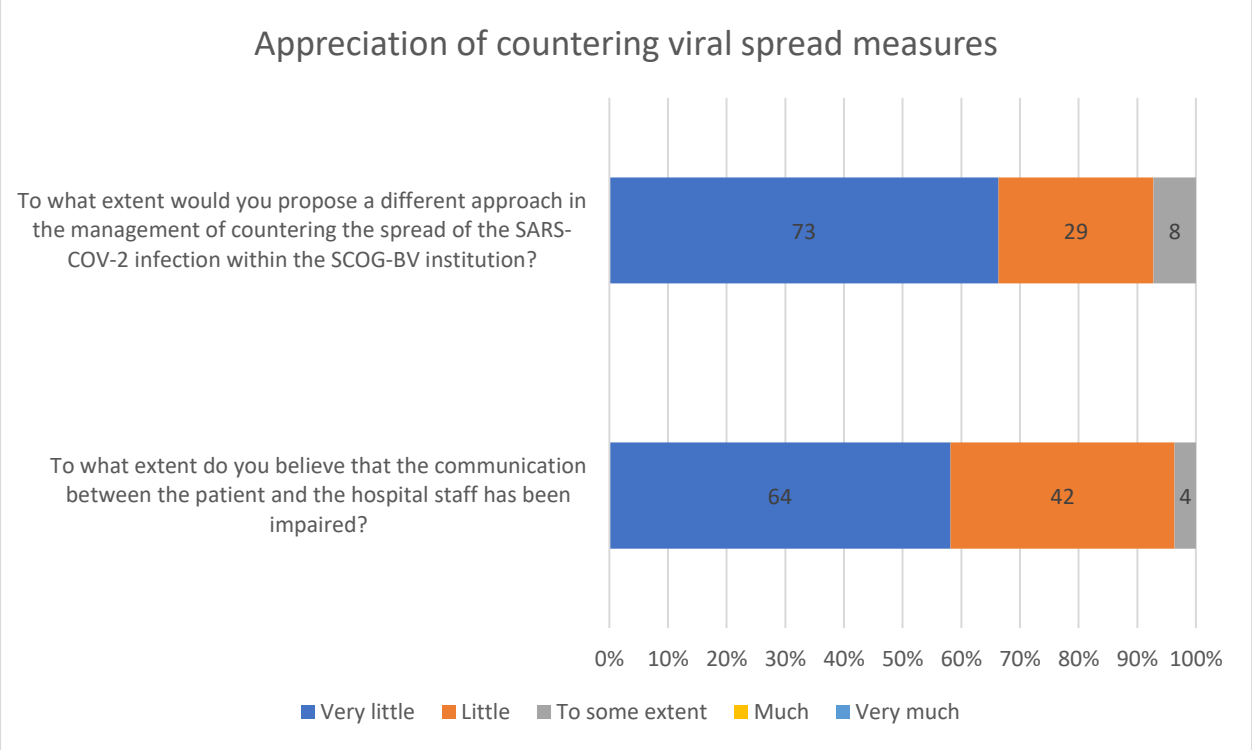

Figure VI-10. The structure of the study group according to the assessment of the measures to combat the SARS-CoV-2 infection and the impact on the doctor-patient relationship

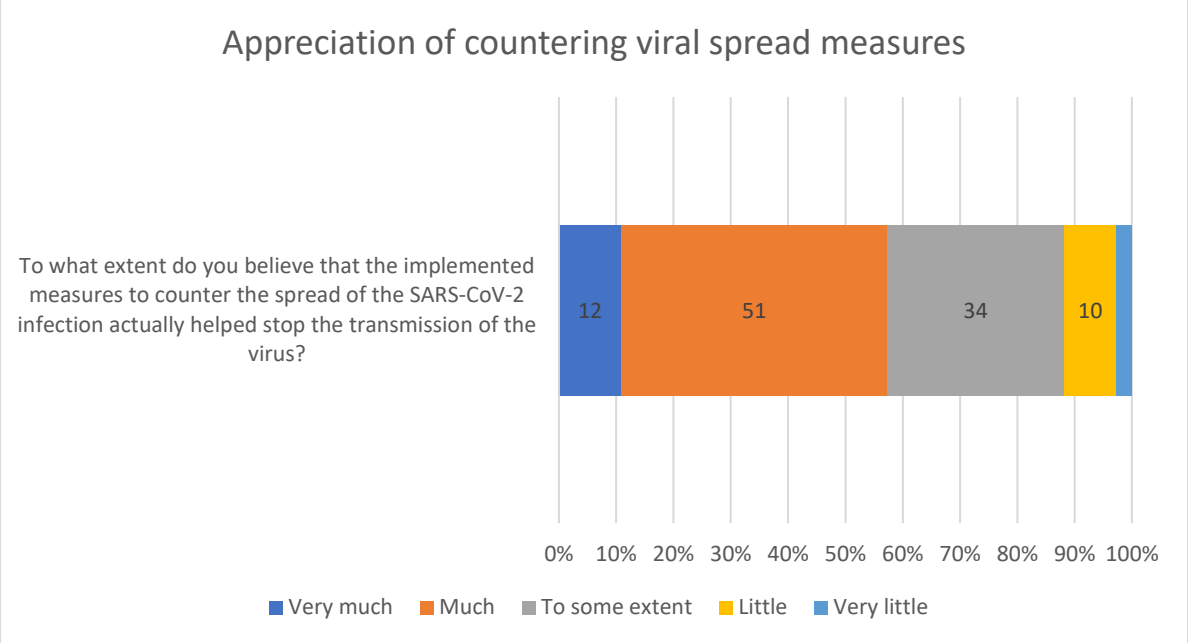

Figure VI-11. The structure of the study group according to the assessment of the measures to combat the SARS-CoV-2 infection

Chapter VII. DISCUSSIONS

Pregnant women have a higher susceptibility to respiratory pathogens due to the anatomical and physiological adaptive changes of the respiratory system that occur during pregnancy, and these viral infections can induce pregnancy complications.

Since the first reports of pneumonia of unknown cause from Wuhan in December 2019 and the subsequent identification of the causative agent as a novel coronavirus now called SARS-CoV-2, there have been more than 180 million cases of coronavirus disease (COVID - 19) and over 4 million attributable deaths globally. Romania has borne a significant proportion of the global burden of COVID-19, with almost 3 million cumulative cases. (Geo-spatial, 2022)

Regarding the incidence of cases, in the current research the upward or downward trend of the number of cases corresponding to our region was respected, so that in 2020 most cases were registered in November (49 obstetric patients), and in 2021 in October (55 obstetric patients).

The spread of the COVID-19 infection occurred rapidly, both in urban and rural environments, thus 52.79% of the patients came from the urban environment, and 47.21% came from the rural environment. Thus, there was no predilection in the spread of the virus, pregnant women from both environments being equally affected.

As the understanding of SARS-CoV-2 infection has developed, concerns have been raised about the effect of COVID-19 on pregnancy. Limited prior experience with SARS-CoV-1 and MERS-CoV has shown an increased risk of adverse pregnancy outcomes, including preterm birth, threatened abortion, and perinatal death. (Daniele Di Mascio et al., 2020) The association of COVID-19 with an unfavorable CD4+ T cell phenotype has raised concerns about implantation and placentation and the possibility of subsequent fetal growth restriction, pregnancy termination, spontaneous abortion and other consequences of placental dysfunction. COVID-19 is also associated with a profound prothrombotic state and, in particular, with the formation of immunogenic thrombi in the microvasculature. (Abou-Ismail et al., 2020) This not only increases the risk of venous thromboembolism, but has been reported by some investigators to lead to high rates of fetal and maternal placental vascular malperfusion, although a subsequent controlled study of placental pathology did not show any specific pattern of pathological features associated with COVID-19. SARS-CoV-2 achieves cell entry by binding to the ACE23 receptor that is expressed in the syncytiotrophoblast and cytotrophoblast and, as such, provides a plausible mechanism for placental infection and vertical transmission to the fetus. (Valdés et al., 2006b)

All these hypotheses materialized in this work, trying to establish which of the complications had a greater impact on the obstetric patients hospitalized in the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" during the pandemic period.

A study conducted in England by Willkinson et al. (Wilkinson et al., 2022) aimed to describe the effect of the COVID-19 pandemic on pregnancy complications at a population level in a multi-ethnic cohort in England. It also examined the effect of confirmed COVID-19 infection on pregnancy outcomes compared to a control group. Among the results obtained, it should be noted that 3,215 (7.4%) babies were born before 37 weeks and 1,030 (2.4%) before 34 weeks. There was no significant change in the risk of preterm birth at less than 37 weeks (OR 1.00, 95% CI 0.91–1.10, p = 0.93) or at less than 34 weeks (OR 1.00, 95% CI 0.85–1.18, p = =0.93) 0.97) in the COVID era compared to the pre-COVID era.

In the research carried out at the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" it was observed that the risk of premature birth was not significantly higher compared to the control group, thus 11.85% of parturients gave birth prematurely, compared to 13, 33% who delivered before 37 weeks (95% CI 0.60-1.29, p=0.58).

The overall cesarean rate was 29.0% in the study by Wilkinson et al. There has been a steady increase in the caesarean section rate over time, with an average increase of 1.6% per calendar year. Adjusting for this increase over time, the risk of caesarean section remained significantly higher during the COVID period (OR 1.11, 95). % CI 1.03–1.19, p = 0.006).

In the current research, a 57% higher rate of caesarean sections could be observed in the group of patients with SARS-CoV-2 infection compared to the control group that recorded 52% cesarean births (p=0.17). Among the indications for caesarean section was SARS-CoV-2 infection (7%), to improve the maternal status in the context of a severe form. Other indications among those studied, with a high weight in the group of patients with COVID infection, were scarred uterus (38%), fetal distress (21%), pelvic presentation in primiparous women (12%) and feto-pelvic disproportions (8%). It is worth noting that fetal distress had a greater weight in the COVID infection group, compared to the control group (8%). This difference may be due to the pathophysiological mechanisms of SARS-CoV-2 infection involved in placental damage. Because the placenta provides support for fetal growth, its histopathology can help elucidate the underlying cause of chronic and acute fetal distress and fetal prognosis. In maternal ischemic conditions, such as those seen in COVID-19 infection, spiral arteries and terminal vessels may not dilate normally and extend into the decidua. Consequently, there is incomplete perfusion of the intervillous space leading to villous damage and possible fetal distress. (Jafari et al., 2021)

In their work, Wilkinson et al reported 116 neonatal deaths and 179 stillbirths (0.26% and 0.41%, respectively). There was no significant change in the risk of stillbirth (OR 0.78, 95% CI 0.51–1.20, p = 0.26) or neonatal death (OR 0.89, 95% CI 0, 54–1.47, p = 0.64) in the COVID era versus the pre-COVID era. (Wilkinson et al., 2022)

In the study carried out at the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" similar results were recorded in terms of fetal death, respectively 0.70% for the control group and 1.26% for pregnant women with SARS-CoV infection -2 (RR 0.55, 95% CI 0.13-2.31, p=0.72).

The association between SARS-CoV-2 infection in the first half of pregnancy and pregnancy loss is still unknown. Infections with other coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), appear to increase the risk of miscarriage.

The overall rate of miscarriage before 20 weeks' gestation ranges from 10% to 26% ("ACOG Practice Bulletin No. 200: Early Pregnancy Loss," 2018) with the rate increasing as the woman ages, reaching approximately 53% in women aged 45 and over. In the study performed by Cavalcante et al. (Cavalcante et al., 2021), the proportion of spontaneous abortion (<22 weeks) in pregnant women with COVID-19 was 15.3% (95% CI 10.95–20.59) and 23.1% (95% CI 13.17–34.95) using fixed and random effects models, respectively. Thus, the spontaneous abortion rate of COVID-19 cases appears to be in the range of the normal pregnant population.

The impact of the pandemic environment on spontaneous abortion rates in two cohorts of pregnant women was studied in Montreal, Quebec, Canada, at two different time points. A retrospective cohort study was conducted to compare the spontaneous abortion rate of all asymptomatic women (without universal screening) in the first trimester during the study period (n = 113, March 13 to May 6, 2020) with that of the cohort control (n = 172, from March 1 to May 17, 2019). There was no significant difference in the total number of pregnancy losses (22.1% vs. 16.9%, p = 0.32) or in each type of miscarriage. (Rotshenker-Olshinka et al., 2021)

In this research, data consistent with the specialized literature were identified, thus in the first trimester of pregnancy there were 3.78% cases of spontaneous abortion in the group with Covid infection and 4.88% in the control group (95% CI 0.67-2.46, p=0.46). Regarding abortion in the second trimester of pregnancy, an insignificant difference was recorded (1.26% in the group with SARS-CoV-2 versus 0.70 in the control group, p=0.72).

Interestingly, the presence of symptoms during the acute phase of COVID-19, the plasma viral load, the severity of the disease and the presence of obstetric risk factors seem to increase the risk of spontaneous abortion in pregnant women infected with SARS-CoV-2.

Regarding the termination of pregnancy in progress in the first and second trimesters, no significant differences were recorded between the two study groups, thus in the group of pregnant women with SARS-CoV-2 infection this event occurred in 1.62 cases, on when in the control group in 3.14% of patients (p=0.20).

It should be noted that during the study period, 1.62% of Covid-positive patients and 3.14% of patients without Covid infection were hospitalized for threatened abortion (p=0.0001), presenting symptoms such as metrorrhagia or pelvic-abdominal pain. The management of these pregnancies included progestogen treatment, supplemented with anticoagulant treatment (low molecular weight heparin) in patients with COVID infection.

The studies suggest that haematological complications are seen more frequently in pregnant women with COVID-19 infection (1.26%) than in pregnant women without (0.45%)

and support the current RCOG advice that all pregnant women hospitalized with confirmed COVID or suspected to receive prophylactic low molecular weight heparin (LMWH) unless delivery is expected in less than 12 hours and continue this for 10 days after discharge. (Servante et al., 2021)

There is some evidence that COVID-19 increases prothrombotic potential in pregnancy. Thrombocytopenia, hypofibrinogenemia, prolonged prothrombin time, prolonged partially activated thromboplastin time, an increase in the level of fibrinogen and D-dimers can accompany both SARS-CoV-2 infection and disseminated intravascular coagulation syndrome. However, in CID syndrome the level of D-dimers significantly exceeds normal values. (Skalska-Świstek et al., 2022).

Regarding the appearance of coagulation disorders in patients admitted to the Obstetrics and Gynecology Clinical Hospital "Dr.I.A.Sbârcea" during the pandemic period, the appearance of changes in coagulation parameters studied in 2.79% of patients with SARS-CoV-2 infection present and in 2.52% of patients in the control group (RR 1.10, 95% CI 0.47-2.53, p= 0.82).

Similar observations were also noted in the study carried out by Khryshchanovich and colleagues who concluded that most of the hematological parameters studied were almost identical both in the group of positive Covid patients and in the control group. At the same time, in patients with symptomatic COVID-19, D-dimer and PCR levels were approximately 2.5 and 6 times higher, respectively, compared to pregnant women without SARS-CoV-2. (Khryshchanovich VY, 2021)

Regarding the vertical transmission of the SARS-CoV-2 infection, in the given research, 3 newborns were infected at the time of birth, respectively 0.54% (p=0.55).

Given the accumulating evidence from studies observing the presence of COVID-19 viral RNA in numerous fetal or neonatal sources and positive serology, vertical transmission of COVID-19 is indeed highly likely. A systematic literature review by Kotlyar et al suggests that maternal infection with COVID-19 in the third trimester appears to be associated with low rates of vertical transmission (approximately 3.2%), with no significant consequences for newborns. (Kotlyar et al., 2021)

We performed a multivariable analysis of certain determinants, including COVID 19 infection, in the occurrence of maternal-child complications. Following this complex analysis, SARS-CoV-2 infection did not have the greatest weight in triggering premature birth, in the occurrence of coagulation disorders, inflammatory syndrome or liver cytolysis. Other infectious, obstetrical, cardiovascular or metabolic factors had a greater impact in the occurrence of maternal-fetal complications.

Particular importance was given to the assessment of the quality of life of patients after SARS-CoV-2 infection, but also of the medical act during the pandemic. To the questions regarding internal infection control management, but also the patient-doctor relationship, most

pregnant women answered that they would not change the already established measures, and communication with the doctor did not suffer in the Obstetrics and Gynecology Clinical Hospital "Dr. I.A. Sbârcea". On the other hand, most hospitalized patients were affected psycho-emotionally by the presence of the SARS-CoV-2 infection, even if the form developed was not severe.

Chapter VIII. CONCLUSIONS

After carrying out this extensive research, which focused on the main maternal-fetal complications that occurred in the context of SARS-Cov-2 infection, we concluded the following:

1. The SARS-CoV-2 infection had a general impact on the medical system and on hospitalized obstetric patients during the pandemic.
2. The hospitalized patients had the environment of origin in equal measure from the rural and urban environment, thus the spread of the infection targeted both environments.
3. SARS-CoV-2 infection does not seem to have a major impact on the occurrence of the studied maternal-fetal complications, not having a determining impact on them.
4. According to the multivariable analysis of the different determining factors, there were other impact factors on maternal-fetal complications.
5. Although the influence of COVID-19 did not have the greatest weight in determining complications, it remains a major factor in determining the way of delivery, and pregnant women with SARS-CoV-2 infection predominantly gave birth by caesarean section.
6. Coagulation and liver cytolysis disorders occurring in the context of COVID-19 remain a landmark for future studies, especially at the pathophysiological level.
7. The inflammatory syndrome that occurs in the SARS-CoV-2 infection seems to be echoed in the severe forms, in the asymptomatic, mild or medium forms it does not change the maternal status.
8. Pregnancy induces a state of physiological hypercoagulability, therefore, in the context of the COVID-19 infection, it is important to anticipate possible complications such as spontaneous abortion or stopping the pregnancy from developing by administering an anticoagulant.
9. A minor difference in the occurrence of maternal-fetal complications between the group with SARS-CoV 2 infection and the one without infection is due to effective medical management, continuously adapting to new changes and new challenges.

Limitations of the study

- One of the main limitations of this study was that the patients were followed in the research only during the hospitalization period, the complications that developed later could not be taken into account
- Following the evolution of newborns with the highlighting of other ways of infection with SARS-CoV-2, such as through breast milk, was not possible
- The detection of SARS-CoV-2 infection at the level of the placenta and the aborted products of conception was not possible from a technical point of view, the laboratory being already clogged with the samples of all infected patients

Chapter IX. PRACTICAL APPLICABILITY OF THE STUDY. PERSONAL CONTRIBUTIONS

The SARS-CoV-2 infection left its mark both in Romania and worldwide, being a virus that changed the entire world map. Studies on this virus carried out on groups of pregnant patients are in continuous research, since the mother-fetus dyad has an important role in the medical society. The research conducted in this thesis is unique because it covered most maternal-fetal complications, starting from hypotheses that were still unclear at the start of the study.

The solutions proposed following the research carried out on this topic:

- Creation of a National Guide aimed at the management of obstetric patients with SARS-CoV-2 infection, depending on the trimester of pregnancy and the severity of the developed form
- Increasing the vaccination rate among obstetric patients, those who are in the process of conception and patients who have given birth
- The constant collaboration of the obstetrician with the doctors in Intensive Care to reduce the percentage of premature births and caesarean sections
- Streamlining the management of medical waste, which increased considerably during the pandemic

Personal expenses:

1. Synthesis contributions

During the research period, I carried out syntheses covering the following topics:

- The epidemiology and structure of the new COVID-19 virus
- Diagnostic methods of the COVID-19 virus
- Symptoms of the COVID-19 virus in pregnant women
- The effect of SARS-CoV-2 infection on pregnancy
- COVID-19 vaccination in pregnancy
- Pathophysiology of the placenta in interaction with SARS-CoV-2 infection
- Immunology of COVID-19 in pregnancy
- Mechanisms involved in spontaneous abortion and stopping the pregnancy from developing

2. Experimental scientific contributions

- Prospective cohort study conducted between January 1, 2020 and March 8, 2022 regarding maternal-fetal complications arising in the context of SARS-Cov-2 virus infection

3. Valorization and dissemination of research results in the academic environment

- Elaboration of scientific research reports every year throughout the research program
- Participation in scientific events with the theme of SARS-CoV-2 infection in pregnancy
- Completion of the doctoral thesis

4. The novelty of the doctoral thesis

- The study of maternal-fetal complications in the context of the new COVID-19 virus, which is under continuous research in the scientific world since it surprised the whole world
- Multivariable analysis of the various potential causes in the occurrence of complications

5. Future research directions

- Continuation of the study with the deepening of the mechanisms that determine the severe forms of infection in the pregnant population
- Continue monitoring of a cohort of discharged patients to evaluate the possible complications in the long term
- Testing placentas and products of conception to demonstrate the context in which vertical transmission of infection occurs.

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Appendix 1 – SUMMARY OF THESIS

ABSTRACT

Introduction: COVID-19 has created a huge challenge in the world's healthcare system. All health systems are vulnerable and there are practical steps that all countries can take, not only to increase the available resources, but also to ensure the ability to adapt and use these resources differently, in the most varied scenarios. This thesis represents a synthesis of the characteristics and maternal-fetal complications that occurred in the context of infection with the SARS-CoV-2 pandemic virus. At the same time, aspects related to epidemiological, clinical data, paraclinical investigations and other parameters of interest were touched upon.

Objectives: The main objective of this thesis is to underline the maternal-fetal complications that occurre during the three trimesters of pregnancy and the obstetrical management applied in order to solve them as efficiently as possible. As specific objectives, the thesis aims to analyze the epidemiological data through the lens of maternal-fetal complications that occurred during the pandemic, to establish potential links between the risk factor of COVID 19 and the multiple complications that occurred at various times during pregnancy (trimester I, trimester II, trimester III) and at the moment of birth, to emphasize aspects concerning the quality of life of patients during the pandemic through the lens of measures to combat the SARS-Cov-2 virus.

Research material and method: The research was carried out in the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" Brașov. This was based on a prospective study carried out over a period of 2 years and 3 months (01.01.2020-08.03.2022). The design of the study involved a cohort, longitudinal, prospective research, which included the population of pregnant women hospitalized during the period mentioned above.

To evaluate the impact of SARS-CoV-2 infection on the quality of life, we created a questionnaire with questions aimed at assessing the general evolution, psycho-emotional damage, the perception of the changes caused by the viral infection, as well as the assessment of intra-hospital measures to combat the transmission of the virus.

The statistical and graphic processing of the data used to carry out the prospective study from January 1, 2020 to March 3, 2023 was carried out with the help of Microsoft Excel, GraphPad prism 9.2.0 and GPOwer3.1 programs.

Results and discussion: The spread of the COVID-19 infection occurred rapidly, both in urban and rural environments, thus 52.79% of the patients came from the urban environment, and 47.21% came from the urban environment. Thus, there was no predilection in the spread of the virus, pregnant women from both environments being equally affected.

In the current research, a 57% higher rate of caesarean sections could be observed in the group of patients with SARS-CoV-2 infection compared to the control group that recorded 52%

cesarean births (p=0.17). Among the indications for caesarean section was SARS CoV-2 infection (7%), to improve the maternal status in the context of a severe form.

In the study carried out at the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" similar results were recorded in terms of fetal death, respectively 0.70% for the control group and 1.26% for pregnant women with SARS-CoV infection -2 (RR 0.55, 95% CI 0.13-2.31, p=0.72).

We performed a multivariable analysis of certain determinants, including COVID 19 infection, in the occurrence of maternal-fetal complications. Following this complex analysis, SARS-CoV-2 infection did not have the greatest weight in triggering premature birth, in the occurrence of coagulation disorders, inflammatory syndrome or liver cytolysis. Other infectious, obstetrical, cardiovascular or metabolic factors had a greater impact in the occurrence of maternal-fetal complications.

Conclusions: The SARS-CoV-2 infection had a general impact on the medical system and on hospitalized obstetric patients during the pandemic, but the SARS-CoV-2 infection does not seem to have a major impact on the occurrence of the studied maternal-fetal complications. According to the multivariable analysis of the different determining factors there were other impact factors on maternal-fetal complications. Although the influence of COVID-19 did not have the greatest weight in determining complications, it remains a major factor in determining the way of delivery, and pregnant women with SARS-CoV-2 infection predominantly gave birth by cesarean section. A minor difference in the occurrence of maternal-fetal complications between the group with SARS-CoV 2 infection and the one without infection is due to effective medical management, continuously adapting to new changes and new challenges.