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The impact of SARS-CoV-2 infection on the mother-fetus binomial

PHD THESIS ABSTRACT

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Introduction

SARS-CoV-2 was first reported in December 2019 in a province in China, and in January 2020, the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a public health emergency of international concern. Within two months, the WHO determined that SARS-CoV-2 infection is a pandemic, reflecting its global spread.

SARS-CoV-2 infection exposes the mother-fetus pair to an increased risk of complications due to physiological changes such as cell-mediated immunity, immaturity of the adaptive immune system, and cytokine dysregulation.

The pregnant woman's body undergoes immunologic changes associated with pregnancy, leading to increased susceptibility to and severity of certain infectious diseases. At the same time, the risk of pre-term delivery may be increased by chronic or acute infections, with about half of preterm births occurring as a result of an inflammatory process.

Various studies have already investigated the impact of the pandemic on pregnancy outcomes, but there is still a lot of uncertainty on this topic, as results vary widely.

All the data and the fact that I was a doctor in a maternity hospital that exclusively cared for SARS-CoV-2 positive pregnancies, led to the creation of several studies to demonstrate the impact of this pandemic on pregnant women and the fetus, but also worth noting is the financial burden on such a hospital.

This paper aims to present the main maternal and fetal complications during pregnancy and a management strategy for pregnant women infected with SARS-Cov-2 and diagnosed during pregnancy, who may develop maternal or fetal complications.

The main objectives of the thesis are to analyze the epidemiological data of SARS-CoV-2 positive patients, to classify each case according to the severity of the disease to establish therapeutic management, to study the epidemiological data through maternal-fetal complications, to establish links between COVID-19 and obstetric complications and to analyze the costs of such a pandemic on a hospital where only SARS-CoV-2 infected patients were treated.

I. GENERAL PART

1. SARS-CoV-2 in the general population

The virus has been named SARS-CoV-2 (severe acute respiratory syndrome caused by coronavirus 2) and the disease caused by coronavirus 2019 (COVID-19). SARS-CoV-2 is an RNA betacoronavirus that infects humans via angiotensin-converting enzyme 2 (ACE2), a receptor on the membrane of epithelial cells [1],[2]. The main route of transmission of SARS-CoV-2 is thought to be respiratory secretions [3].

1.1 Symptomatology

The possibility of SARS-CoV-2 infection should be considered in anyone with fever and/or new-onset respiratory symptoms. Although cough and dyspnoea are considered the classic elements of COVID-19, other respiratory symptoms, such as odynophagia, rhinorrhea, and nasal congestion, are frequently reported as the only symptoms indicative of COVID-19. Other commonly encountered clinical manifestations include anosmia, ageusia, myalgias, and diarrhea [4].

1.2 Diagnosis

A viral test is required to diagnose SARS-CoV-2 infection: either an antigen test or a nucleic acid amplification test (NAAT), the most commonly used being RT-PCR, a reverse transcription polymerase chain reaction test. NAAT is preferred due to its superior sensitivity [5],[6],[7], but antigen tests are more affordable, provide faster results than NAAT [8],[9],[10], and are a good alternative, as long as subjects consider the need to repeat the test to optimize sensitivity.

1.3 Management and treatment

Outpatient management is appropriate for most patients with COVID-19.

To assess the prognosis of the disease and to identify a possible organ dysfunction it is necessary to check the following hematologic parameters: complete blood count (CBC) with total lymphocyte count, basic metabolic panel, liver panel, C-reactive protein (CRP), lactate dehydrogenase (LDH), prothrombin time (PT), partial thromboplastin time (APTT), fibrinogen, D-dimer. A thoracic radiologic examination is performed by radiography or computed tomography (CT) [11].

For patients with documented COVID-19, empiric treatment for bacterial pneumonia is not routinely given but may be considered for community-acquired pneumonia. Procalcitonin

may be a suggestive marker for bacterial pneumonia, although it has been described to be elevated in COVID-19 [12],[13],[14],[15].

Venous thromboembolism prophylaxis should be performed for all patients hospitalized with COVID-19. Dose intensity is based on an individualized assessment of thrombotic and hemorrhagic risk [16],[17],[18]. For patients with risk factors for severe disease who have been hospitalized for COVID-19, antiviral treatment with Remdesivir is indicated [19],[20],[21].

For patients who do not require oxygen and who have no risk factors for progression to severe disease, symptomatic treatment is recommended.

Supplemental oxygenation with a low-flow system via nasal cannulae is generally sufficient [22],[23]. Options for patients who require more advanced support than low-flow oxygen, but who do not yet require intubation, include non-invasive ventilation (NIV, including continuous positive airway ventilation and bilevel positive airway ventilation) and high-flow oxygen via nasal cannula (HFNC) [24],[25].

1.4 Vaccination

Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach to contain the COVID-19 pandemic. Several COVID-19 vaccines are available worldwide.

Vaccination appears to further boost antibody levels and cell-mediated responses in those with previous infection and likely enhances the durability and extent of protection [26],[27],[28].

2. SARS-CoV-2 in pregnancy

2.1 The impact of SARS-CoV-2 infection on the mother-fetus binomial

Given the cardiovascular, pulmonary, hormonal, and immunologic changes associated with pregnancy, pregnant women are considered to be at higher risk during the pandemic [1],[2],[3],[29],[30],[31],[32]. Specifically, hormonal fluctuations and the prevalence of a Th2 cell-mediated immunologic environment increase the susceptibility of pregnant women to infection, while the increased oxygen requirements of the pregnant woman, together with decreased lung capacity due to a high diaphragm, reduce women's tolerance to hypoxia and dyspnea. Thus, infection of pregnant women with SARS-CoV-2 has been associated with more severe morbidity affecting both mother and fetus [33],[34],[35],[36].

2.2 Impact of SARS-CoV-2 on the mother

As mentioned above, COVID-19 is a severe infectious disease, particularly among pregnant women, who are considered a high-risk group, as there is always the possibility of developing all the above symptoms along with complications. ARDS (acute respiratory distress syndrome) is the most common and most serious complication, followed by sepsis and septic shock, acute kidney injury, and acute cardiac injury [37]. In addition, infected pregnant women are more likely to be admitted to an intensive care unit than pregnant women who are not ill [4] with a risk of death in case of deterioration of maternal condition [4],[38],[39]. Some studies have also reported several other complications of pregnancy such as preeclampsia, gestational diabetes, hypertensive disorders, hypothyroidism, and anemia, but no firm conclusion could be reached in coordination with COVID-19 [1],[3],[30],[40],[41],[42],[43].

2.3 Impact of SARS-CoV-2 on the fetus

SARS-CoV-2 infection during pregnancy can also directly affect the fetus. First, cases of spontaneous abortions and perinatal deaths have been reported. Preterm births that are largely iatrogenic appear to be two to three times more frequent than background births in women with symptomatic COVID-19 [44]. Capobianco's analysis noted that preterm births occurred in almost all studies, by an average of 23% of cases [30]. Several other studies confirmed that the rate of preterm births among SARS-CoV-2-infected pregnant women ranged from 25 to 44% [45],[46],[47],[48],[49].

2.4 Time and type of birth

It should be noted that COVID-19 does not adversely affect the majority of pregnancies.To prevent fetal mortality and possibly improve maternal cardiopulmonary function, controlled cesarean delivery is indicated when the respiratory status is too critical to manage, particularly after 28 weeks gestation. Reasons include maternal dyspnea and hypoxia, fetal distress, or perinatal transmission concerns [42],[43],[50].

2.5 SARS-CoV-2 infection and vertical transmission

Despite the high rate of cesarean births, vaginal birth should be preferred when possible, taking into account that most results do not seem to prove vertical transmission [1],[51],[52].

2.6 Impact of SARS-CoV-2 infection on the placenta

The term SARS-CoV-2 placentitis is used to define the coexistence of three microscopic elements: chronic histiocytic intervilocytosis, large fibrin deposits and trophoblast necrosis,

which have been associated with perinatal death after maternal SARS-CoV-2 infection, even in uninfected fetuses and neonates [53].

2.7 Vaccination against SARS-CoV-2 in pregnancy

Vaccination of pregnant women reduces the increase in maternal and fetal morbidity associated with COVID-19 [28]; therefore, all pregnant women should be vaccinated in parallel with the rest of the population, depending on their age group and comorbidities. The Center for Disease Control and Prevention (CDC), the Royal College of Obstetricians and Gynecologists (RCOG), the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine, and the American College of Obstetricians and Gynecologists (ACOG) all recommend vaccination of all pregnant women [54],[55].

II.PERSONAL CONTRIBUTIONS

3. Working hypothesis and general objectives

Working hypothesis

This research work was carried out to investigate the complex impact of SARS-CoV-2 infection on the mother-fetus binomial, with a focus on the increased risk of preterm birth, the effect of this virus on the placenta together with all the consequences of this damage such as intrauterine growth restriction, antepartum and intrapartum fetal hypoxia, abortion and even fetal death in utero, as well as on the financial implications that the 2 years of the pandemic had on the exclusive COVID centers, a unique situation in Romania, in which the Bucur Maternity Hospital was included.

The working hypothesis assumes that SARS-CoV-2 infection increases the risk of medically induced preterm birth due to complications affecting maternal and fetal status, leads to specific histopathologic changes in the placenta that contribute to preterm birth and other complications of pregnancy, and imposes significant costs for centers exclusively dedicated to these cases, raising the question of whether the dedication of some health facilities to exclusively treat patients with other pathology but associated with SARS-CoV-2 infection is justified under the cost/benefit ratio.

General objectives

1. Investigation of clinical and paraclinical factors in COVID-19-positive pregnant women that may lead to preterm delivery by:

- Analysis of the frequency and causes of preterm births in pregnant women infected with SARS-CoV-2 compared to uninfected pregnant women.
- To determine the decision-making processes involved in choosing preterm birth in these cases.

2. Assessing the impact of SARS-CoV-2 infection on the placenta by:

- Histopathologic examination of the placenta in COVID-19 positive pregnancies.
- Assess the relationship between placental changes and complications of pregnancy, in particular preterm birth.

3. Economic impact assessment of an exclusive tertiary COVID-19 center :

- Estimating the additional costs incurred by a health care center dedicated exclusively to the management of COVID-19 positive pregnant patients.
- Comparison of these costs with those for care of pregnant patients not infected with SARS-CoV-2.

4. Research methodology

Data collection for this research work was conducted from March 19, 2020 to March 12, 2022. The main aim of the research was to assess the impact of SARS-CoV-2 infection on the mother-fetus binomial from clinical, paraclinical, and economic perspectives.

The patients were recruited from Bucur Maternity, St. John Hospital, Bucharest.

On March 19, 2020, following a decision of the Ministry of Health, it was designated as a COVID-19 tertiary maternity hospital. Thus, Bucur Maternity Hospital exclusively treated patients with obstetric or gynecological problems positive for SARS-CoV-2.

Our obstetrics department typically handles approximately 2000-2200 births per year. During the period in which Bucur Maternity Hospital exclusively treated COVID-19 patients, more than 2400 assessments were registered in the emergency department and 635 deliveries were attended for COVID-19 patients. Bucur Maternity Hospital had specific protocols in place during the pandemic regarding admission and discharge of patients. During the period March 19, 2020 - March 12, 2022, Bucur Maternity Hospital admitted COVID-19 patients exclusively, except for the period July 1, 2021 - October 1, 2021, when both COVID-19 and non-COVID-19 patients were hospitalized based on the Ministry of Health guidelines.

In terms of methodology, the studies were prospective cohort studies, conducted in comparison with uninfected pregnant patients.

All data were extracted from the patient's electronic records, observation sheets, and birth and operative records drawn up during this period.

Thus, 3 studies were conducted to assess the impact of COVID-19 in pregnancy, respectively:

- **Study I-** which included 286 COVID-19 and 124 non-COVID-19 patients to analyze the impact of SARS-CoV-2 infection on preterm delivery.

- **Study II-** in which 78 SARS-CoV-2 infected patients who gave birth preterm and 78 uninfected patients were selected to evaluate the influence of SARS-CoV-2 on the placenta in preterm deliveries.

- **Study III-** consisted of 422 patients positive for SARS-CoV-2 and a control group of 174 non-COVID-19 patients to explore the financial impact of the pandemic for a center exclusively caring for COVID-19 positive pregnant women.

All patients included in the studies signed consents for medical acts and participation in medical education.

Before the research, the study protocol was approved by the "Ethics Committee" of the "St. John's Emergency Clinical Hospital St. John" no. 30386/16.12.2021.

Statistical analysis was performed using the IBM SPSS Statistics 21 program, and $p \leq 0.05$ values were considered statistically significant.

5. The impact of SARS-CoV-2 infection on preterm delivery - the experience of an exclusive COVID center

5.1. Introduction

The maternal and perinatal impact of the COVID-19 pandemic has already been the subject of numerous publications and meta-analyses. Pregnant women are at increased risk of developing severe or critical forms of SARS-CoV-2 disease [56]. Although the majority of cases are asymptomatic or mild, data indicate an increased risk of complications, including death, compared to non-pregnant women [44]. Studies indicate an increased frequency of pregnancy-associated complications, including prematurity, pre-eclampsia, and fetal death in utero [57].

This study aimed to evaluate the link between SARS-CoV-2 infection and preterm delivery in a tertiary center.

5.2. Material and methods

The objective of the study was to assess the impact of SARS-CoV-2 infection on preterm deliveries in a COVID-only tertiary center.

A prospective study was conducted to compare the course of pregnancy in pregnant patients positive for SARS-CoV-2 infection versus a similar sample of uninfected pregnant women. The patients included in the two groups were recruited from Bucur Maternity, St. John's Hospital, Bucharest. In the study, patients for both the study and control groups were selected between 03.06.2021 and 17.03.2022, after signing informed consent. **The inclusion criteria** were as follows: patients over 18 years of age, pregnant women with a positive RT-PCR or antigen-positive test for SARS-CoV-2, gestational age between 24 and 41 weeks, singleton pregnancy, hospitalization for a minimum of 24 hours, delivery in our unit. **Exclusion criteria** for both groups included: refusal to participate in the study, minor patients, preterm delivery in the history, multiple pregnancies, pregnant women hospitalized for obstetric conditions who did not deliver in our clinic, and patients discharged before 24 hours.

5.3. Results

After applying the inclusion and exclusion criteria, the study included 410 pregnant patients, divided into two groups: a group of 286 COVID patients and a control group of 124 non-COVID patients.

Table 5.1: Characteristics of patients in the group

Maternal characteristics	COVID-19 (n=286)	Non-COVID-19 (n=124)
Maternal age (years, %)	18 - 30 - 49.22%	18 - 30 - 45.16%
	31 - 40 - 47.67%	31 - 40 - 46.77%
	Over 40 - 3.10%	Over 40 - 8.06%
Gesta (no. - %)	1 - 40.56%	1 - 33.06%
	2 - 30.42%	2 - 31.45%
	≥3 - 29.02%	≥3 - 35.48%
Para (no. - %)	1 - 53.85%	1 - 41.94%
	2 - 36.36%	2 - 35.48%
	≥3 - 9.79%	≥3 - 22.58%
VG (weeks - %)	<28 weeks - 2.63%	<28 weeks - 11.54%

	28 - 31 July - 7.89%	28 - 31 July - 15.38%
	32 - 36 weeks - 89.47%	32 - 36 weeks - 73.08%
Births (%)	Spontaneous - 14.69%	Spontaneous - 41.13%
	Caesarean - 85.31%	Caesarean - 58.87%

In **COVID patients who delivered prematurely**, the indication for cesarean section was given due to: hypertonia - 2.86% of cases, abnormal presentation - 14.29%, fetal distress - 20%(n=7), post-cesarean scar uterus - 8.57%, maternal deterioration (n=11) - 31.43%, for other reasons - 22.86%(n=8), and in the case of **non-COVID patients who delivered prematurely**, the indication for cesarean section was given due to: abnormal presentation - 21.05% of cases, fetal distress - 26.32%, post-cesarean scar uterus - 21.58%, for other reasons - 31.58%. In pregnant women with severe COVID: 81.25% of the NN were discharged from the maternity ward with a favorable outcome, but 12.50% required transfer to another hospital unit, 6.25% died, and in pregnant women with mild/moderate COVID: 99.25% of the NN were discharged from the maternity ward with a favorable outcome, but 0.38% required transfer to another hospital unit, respectively 0.38% died. Both in general and in preterm births, the severity of COVID-19 symptoms was associated with delivery at a lower gestational age. Symptomatic patients delivered in 88.64% of cases by cesarean section (n=78) and in 11.36% of cases spontaneously (n=10), whereas asymptomatic patients delivered in 83.84% of cases by cesarean section (n=166) and in 16.93.75% of severe cases delivered by cesarean section (n=15), and only 6.25% spontaneously (n=10), and 84.81% of mild and moderate cases delivered by cesarean section (n=229), and 15.19% spontaneously (n=41). There was a statistically significant association between COVID severity and preterm delivery, χ^2 =45.251, p≤0.001. There is a statistically significant association between leukocyte level and preterm delivery, χ^2 =7.580, p=0.023. The application of a Mann-Whitney U test indicated that pregnant women who delivered preterm had significantly higher levels of CRP (U=1670.00, Z=-3.504, p≤0.001). Pregnant women who delivered preterm had significantly higher levels of procalcitonin (U=177.500, Z=-2.914, p=0.004).

5.4. Discussions

We could observe a significant increase in the rate of cesarean deliveries in the COVID-19 group (85.31%) compared to the control group (41.13%), a result also found in a meta-

analysis by Smith et al. [58], and an incidence of 84.21% among premature births compared to 73.08% in the negative group. It can thus be said that patients infected with SARS-CoV-2 are at increased risk of preterm birth by increasing the number of iatrogenic births, a result also observed by Bahado et al. in a 2022 meta-analysis [59].

Our study demonstrates once again that for all births, as well as for preterm births, the severity of symptomatology led to delivery at lower gestational ages ($p \leq 0.001$). A potential mechanism that could explain the unfavorable course of SARS-CoV-2 infections at lower gestational age is the increased level of angiotensin-converting enzyme 2 (ACE2) in the placenta at an early gestational age [60].

5.5. Conclusions

In our study, the overall percentage of preterm births was not significantly increased among SARS-CoV-2 positive pregnant women compared to uninfected patients. However, there was a notable increase in the incidence of cesarean deliveries, particularly preterm cesarean deliveries, often performed to improve maternal and fetal outcomes in the context of COVID-19. The severity of symptoms was correlated with a higher likelihood of preterm cesarean delivery, performed to manage complications and reduce risks associated with infection. Moderately severe forms of COVID-19 were associated with delivery at a lower gestational age. Pregnant women with COVID-19 who delivered preterm had higher levels of inflammatory markers, particularly leukocyte and neutrophil counts, compared with those who were negative for COVID-19, and C-reactive protein (CRP) and procalcitonin levels were significantly elevated in COVID-19-positive patients who delivered preterm, suggesting that these biomarkers may serve as indicators of the severity of infection and inflammatory status in this group.

The data from our study led to the conclusion that SARS-CoV-2 infection is a risk factor for preterm birth because of its clinical implications, but it did not result in a higher incidence of preterm birth than in cases negative for infection. The severity and symptomatology of COVID-19 are, however, determinants of increased risk of prematurity, especially by determining iatrogenic delivery by cesarean section to improve the outcome of positive patients.

6. Placenta as a key witness of SARS-CoV-2 infection in preterm births

6.1. Introduction

SARS-CoV-2 has been found to bind via angiotensin II converting enzyme (ACE2) to the cell membrane of target host cells [61]. ACE2 is expressed in most organs, including the placenta, syncytiotrophoblast, cytotrophoblast, decidual stromal cells, endothelial smooth muscle cells, vascular cells and decidual perivascular cells [62]. Co-expression of ACE2 and TMPRSS2 receptors in the placenta may increase the vulnerability of the placenta and fetus to SARS-CoV-2 infection [63].

This study aimed to identify placental histopathologic changes in preterm birth and their impact on preterm delivery in pregnancies with SARS-CoV-2 infection.

6.2. Material and methods

The objective of the study was to assess the impact of SARS-CoV-2 infection on the placenta, based on the hypothesis that the placenta is a site of virus attachment and a barrier to transmission to the fetus. However, the placental histopathologic changes caused by this virus have consequences on the course of pregnancy and the fetus, including the induction of preterm delivery in these pregnant women.

We conducted a prospective study comparing histopathologic aspects of placentas and pregnancy outcomes in SARS-CoV-2 positive and uninfected pregnant women. The recruitment of COVID-19 positive patients was done in Bucur maternity hospital, an exclusive COVID tertiary center, between 20.03.2020 and 20.03.2022, after signing informed consent and cases for the control group were drawn from 19.03.2018 to 19.03.2020. **Inclusion criteria for** the study were: gestational age between 24 to 36 completed weeks, attestation of infection status during pregnancy by RT-PCR or positive SARS-CoV-2 rapid Antigen test, macro and microscopic histopathologic examination of placenta available. **Exclusion criteria** were: refusal of any type of investigation or treatment, documentation of congenital malformations that may influence the course of pregnancy, preterm delivery in the antecedents, to eliminate possible biases determined by risk factors in the history.

6.3. Results

Following the application of inclusion and exclusion criteria, the study comprised 2 study groups of COVID and non-COVID patients, consisting of a total of 156 patients, 78 COVID-19 positive patients who delivered prematurely and 78 non-COVID-19 patients who delivered

prematurely. The two groups of patients were similar in age. Among the COVID patients, 79.49% had a gestational age of 32-36 weeks (n=62), 12.82% of them had a gestational age of 28-31 weeks (n=10), and 7.69% of them had a gestational age of less than 28 weeks (n=6). There was a statistically significant association between COVID infection and infarction, χ^2 =8.690, p=0.003, and the relationship between the two variables was direct and moderate in intensity (p=0.003). 58.97% of COVID (n=46) and 46.15% of non-COVID (n=36) pregnancies had fibrinoid deposits. There was a significantly higher incidence of decidual arteriopathy among COVID pregnancies, occurring in 2 out of 3 COVID (66.67%, n=52) and less than 1 out of 4 non-COVID (23.08%, n=26) pregnancies, respectively. There was a statistically significant association between the need for oxygen therapy and the presence of decidual arteriopathy (χ^2 =5.850, p=0.016). The presence of intervillous thrombi was found in 53.85% of COVID and 38.46% of non-COVID pregnant women. A significantly higher incidence of inflammatory infiltrate was observed among the placentas of COVID-positive pregnancies. Thus, 69.23% of them showed inflammatory infiltrate, while among the negative pregnancies, 46.15% showed inflammatory infiltrate. Chorioangiogenesis was present in 17.95% of COVID-19 and 10.26% of non-COVID pregnancies, respectively. 23.08% of COVID-19 and 28.21% of non-COVID pregnancies showed villous maturation. 74.36% of COVID-19 pregnancies showed placental changes suggestive of maternal vascular malperfusion (MVM).

6.4. Discussion

During the pandemic, a triad of placental histopathologic changes referred to as SARS-CoV-2 placentitis [64],[65] has been reported in a series of case studies. The triad includes trophoblast necrosis, intervillous inflammatory infiltrates, and fibrinoid deposits [66].

The objective of this study was to identify whether there are specific placental histopathologic changes specific for SARS-CoV-2 infection in preterm births or rather placental changes that caused preterm delivery.

According to the study over 50% of the placentas had weight ≤ 10th percentile (placental hypoplasia), placentas had significant areas of infarction in 64.1% of COVID cases, decidual arteriopathy in 66.67% of cases, inflammatory infiltrate in 69.23% of cases, fibrinoid deposits in 58.99% of cases and chorangiosis in about 18% of cases, all found in moderately and significantly higher proportions than in non-COVID cases. In COVID-19 pregnant women with

low oxygen saturation who required supplemental oxygen therapy or intubation, these lesions were statistically significantly associated [67].

6.5. Conclusions

This study reports several lesions such as infarcts, decidual arteriopathy, fibrinoid deposition, inflammatory infiltrate, chorangiosis, and MVM lesions, but also the occurrence of intervillous thrombi which is an MVF lesion as a possible cause of preterm delivery.

Placentas from COVID-19-positive pregnancies, especially those in moderate and severe forms of disease that required oxygen therapy or intubation, had significantly lower weights compared with those from COVID-19-negative cases. There was a higher incidence of placental infarcts, particularly at younger gestational ages and in severe COVID-19 cases associated with fibrinoid deposits, indicating an increased risk of placental insufficiency and compromised fetal oxygenation. Pregnant women with COVID-19, particularly those with severe disease, showed placental changes such as decidual arteriopathy and intervillous thrombi, suggesting a negative impact of COVID-19 on the maternal-fetal interface that could contribute to the unfavorable outcome of pregnancy. Chorangiosis was found predominantly in severe cases of COVID-19. This condition reflects an adaptive response to hypoxia or other stressors affecting placental function. A significant proportion of SARS-CoV-2-infected pregnant women had placental changes consistent with maternal vascular malperfusion, emphasizing the potential of this virus to exacerbate conditions leading to placental hypoxia and impaired nutrient supply to the fetus. The placental abnormalities observed probably contribute to the increased incidence of preterm delivery in COVID-19 positive pregnancies by compromising placental function, thus leading to iatrogenic delivery for fetal well-being.

During the COVID-19 pandemic, multiple studies have been carried out demonstrating the impact of SARS-CoV-2 infection on pregnancy, with many of the specific complications being caused by placental changes. Specific lesions of maternal vascular malperfusion as well as lesions of fetal vascular malperfusion have been reported. Our study provides strong arguments to support the proposed term SARS-CoV-2 placentitis.

7. The financial burden of pregnant women with SARS-CoV-2 in a COVID-19 exclusive tertiary maternity unit

7.1. Introduction

The SARS-CoV-2 pandemic has had a considerable impact on health systems around the world, and Romania was no exception [68]. The impact on health care costs for pregnant women has been considerable, especially in tertiary centers for SARS-CoV-2 cases only [69].

The aim of this study was to assess the impact of SARS-CoV-2 infection on healthcare costs by analyzing case management in Bucur maternity hospital, exclusively COVID-19.

7.2. Material and methods

The objective of the study was to analyze whether the model adopted by the NHS of complete separation of obstetric care for COVID-19 and non-COVID-19 patients had a significant impact on the costs for our hospital, thus assessing the efficiency of taking a hospital out of the general circuit and allocating it exclusively to infected patients. We conducted a prospective study in which we compared the costs of caring for two groups of patients: a group of pregnant women infected with SARS-CoV-2 (the study group) with a control group of uninfected pregnant women.

In the research, patients included in the study group were selected from March 2020 to March 2022 after signing informed consent. **The inclusion criteria** for the study group were as follows: pregnant women with a positive RT-PCR or antigen-positive test for SARS-CoV-2, gestational age between 24 and 41 weeks, hospitalization for a minimum of 24 hours, and delivery in our unit.

To assess the impact of SARS-CoV-2 infection on costs, we compared data from infected patients with a control group consisting of pregnant women who gave birth at Bucur Maternity Hospital between January 2019 and January 2020, and between July 1, 2021 and October 1, 2021, the interval when the unit was temporarily out of the COVID-exclusive circuit, that is, between the two major waves of the pandemic in our country. The inclusion criteria for the control group were similar: gestational age between 24 and 41 weeks and delivery at our unit. **Exclusion criteria** for both groups included: refusal to participate, pregnant women hospitalized for obstetric conditions who did not deliver in our clinic, and patients discharged before 24 hours.

7.3. Results

Following the application of the inclusion and exclusion criteria, the study included 818 patients, divided into two groups: a group of 412 COVID-19 patients and a control group of 406 non-COVID-19 patients.

COVID patients delivered mostly by cesarean section - in 83.46% of cases (n=338), only 16.54% of them delivered spontaneously (n=67). **Non-COVID patients** delivered frequently both by cesarean section - in 58.54% of cases (n=114) and spontaneously - in 41.46% of the cases (n=102). In the case of **COVID patients**, the average settlement per patient was 12863.43 RON, the average hospitalization cost per patient was 9778.28 RON, the average cost of medicines per patient was 2576.39 RON, the average cost of sanitary materials used per patient was 745.48 RON, and the average cost of tests per patient was 482.95 RON. In the case of **non-COVID patients**, the average bill per patient was 8723.58 RON, the average hospitalization cost per patient was 9778.28 RON, the average cost of medicines per patient was 163.39 RON, the average cost of sanitary materials used per patient was 125.30 RON, and the average cost of tests per patient was 127.69 RON.

Table 7.1: Detailed expenditure by type of birth

Parameters	**COVID-19 patients (n=412)**		**Non-COVID-19 patients (n=406)**	
Type of birth	Cesarean section	Spontaneous	Cesarean section	Spontaneous
Hospitalization expenditure (RON, average, ranges)	10287.13 (1493.56-38061.70)	8565.14 (1870.78-18549.44)	9690.96 (3741.56-24320.14)	7654.54 (1309.46-29932.48)
Treatment expenditure (RON, average, ranges)	2984.25 (13.18-13519.02)	907.29 (22.32-9078.20)	268.06 (10.33-19191.26)	75.67 (11.90-244.59)
Sanitary materials (RON, averages, ranges)	856.82 (44.21-4781.81)	427.13 (39.01-1713.38)	184.35 (6.86- 1705.27)	90.14 (18- 321.89)
Laboratory analysis (RON, average, ranges)	568.74 (39.00-5825.92)	229.92 (40.48-437.09)	154.09 (12.18- 808.77)	103.06 (31.24-539.22)

Total expenditure (RON, average, ranges)	13943.63 (2385.23-50494.93)	9680.17 (2028.54-21270.85)	10380 (4019.47-25112.23)	8204.46 (2014.39-30557.40)

The total settlement of severe cases was on average 1.8 times (by 80%) higher than that of a low severity case, respectively 2.4 times (by 140%) higher than a non-COVID case (21049.89 RON vs. 11246 RON vs. 8723.58 RON) (p=0.048). The hospitalization costs of severe cases were on average 1.5 times (by 50%) higher than a low severity case, respectively 1.6 times (by 60%) higher than a non-COVID case (13418.16 RON vs. 9002.64 RON vs. 8121.94 RON). Medication costs of severe cases were on average 3.3 times (by 230%) higher than a low severity case, respectively 37.2 times (by 3620%) higher than a non-COVID case (6253.01 RON vs. 1887.62 RON vs. 163.39 RON). The expenditure on sanitary materials of severe cases was on average 2.6 times (by 160%) higher than a low severity case, respectively 12.5 times (by 1150%) higher than a non-COVID case (1567.03 RON vs. 604.14 RON vs. 125.30 RON). Laboratory costs for laboratory tests of severe cases were on average 3.5 times (by 250%) higher than for a low-severe case, respectively 9.97 times (by 897%) higher than for a non-COVID case (1274.03 RON vs. 362.99 RON vs. 127.69 RON).

7.4. Discussion

In this study, we reported the expenditures, hospitalization days of COVID-19 patients, and changes in healthcare services caused by the COVID-19 pandemic in a tertiary center in Romania. The objective of this study was to highlight the impact of SARS-CoV-2 infection on health system resources from the perspective of a maternity hospital exclusively for SARS-COV-2 patients. Analysis of the parameters showed a significant increase in hospitalization, medication, and investigation costs, correlated with increased severity of the disease, but also compared to uninfected pregnant women. There was a significantly higher incidence of cesarean deliveries among COVID patients (83.4%) compared to non-COVID patients (58.54%), as well as an increase in the percentage of premature cesarean deliveries, results also found in other studies [44],[58],[70],[71],[72]. Remarkable are the significant differences between the expenses of a severe case compared to a less severe or a non-COVID case, and we can exemplify by the total settlement of severe cases that were on average 80% higher than a less severe case, respectively 140% higher than a non-COVID case (21049.89 RON vs. 11246 RON vs. 8723.58

RON) (p=0.048). This finding is extremely worrisome for public hospitals, which are fundamental for achieving universal healthcare [73].

7.5. Conclusions

Both COVID-19-positive patients and their newborns required prolonged periods of hospitalization compared to non-COVID-positive cases, generating a primary additional cost driver. Medications often used to manage moderate and severe symptoms, but also to prevent complications, have significantly increased overall drug costs. The diagnostic protocols for COVID-19 positive patients involved a wider range of laboratory tests and paraclinical investigations and the repetition of these tests to monitor the health of the mother and fetus contributed to increased healthcare costs. The need for more protective measures for medical staff has driven up costs even further.

The study found that in severe cases of COVID-19, the costs were 80% higher compared to mild cases and 140% higher compared to non-COVID patients. This disparity underscores the financial impact of case severity on medical resources, highlighting the need for efficient resource allocation and management.

8. Conclusions and personal contributions

8.1. Conclusions

Given the aim of this work to assess the impact of SARS-CoV-2 infection on the mother-fetus binomial by identifying maternal and fetal complications, as well as the economic impact of the pandemic caused by this virus on a health care center for pregnant women and newborns, we have reached the following conclusions that we have established:

1. The overall percentage of preterm births was not significantly increased among SARS-CoV-2 positive pregnant women compared to uninfected patients. However, there was a notable increase in the incidence of cesarean section deliveries, particularly preterm cesarean section deliveries, which were often performed to improve maternal and fetal outcomes in the context of COVID-19.
2. The presence of COVID-19 symptoms in pregnant women was a determining factor in the timing and method of delivery. In particular, the severity of symptoms was correlated with a higher likelihood of preterm delivery by cesarean section, performed to manage complications and reduce the risks associated with infection.

3. In both term and preterm deliveries, the more severe form of COVID-19 was associated with delivery at a lower gestational age. This suggests that clinical management of pregnant women with severe symptoms may require earlier deliveries to reduce risks to maternal and fetal health.
4. Pregnant women with COVID-19 who gave birth preterm had higher levels of inflammatory markers, particularly leukocyte and neutrophil counts, compared with those who were negative for COVID-19.
5. In particular, levels of C-reactive protein (CRP) and procalcitonin were significantly elevated in COVID-19-positive patients who delivered preterm, suggesting that these biomarkers may serve as indicators of the severity of infection and inflammatory status in this group.
6. Although they had a lower Apgar score at birth and were born at younger gestational ages, newborns born to COVID-19 positive mothers had a favorable outcome in more than 90% of cases.
7. Placentas from COVID-19-positive pregnancies, especially those in moderate and severe forms of disease that required oxygen therapy or intubation, had significantly lower weights compared with those from COVID-19-negative cases. This suggests a potential impact of the virus or maternal health-related parameters on the development of placental function.
8. There was a higher incidence of placental infarcts, particularly at younger gestational ages and in severe cases of COVID-19. The fibrinoid deposits associated with these infarcts, observed more frequently in severe forms of the disease, indicate an increased risk of placental insufficiency and compromised fetal oxygenation.
9. Pregnant women with COVID-19, especially those with severe disease, showed placental changes such as decidual arteriopathy and intervillous thrombi. These changes were more common at lower gestational ages, suggesting a negative impact of COVID-19 on the maternal-fetal interface that may contribute to the unfavorable pregnancy outcome.
10. Chorangiosis, a condition characterized by the proliferation of capillaries in the chorionic villi, has been found predominantly in severe cases of COVID-19. This condition reflects an adaptive response to hypoxia or other stressors affecting placental function.
11. A significant proportion, 3 out of 4 pregnant women infected with SARS-CoV-2 had placental changes consistent with maternal vascular malperfusion, emphasizing the potential of this virus to exacerbate conditions leading to placental hypoxia and impaired nutrient supply to the fetus.

12. The placental abnormalities observed probably contribute to the increased incidence of preterm delivery in COVID-19 positive pregnancies by compromising placental function, thus causing iatrogenic delivery for fetal well-being.
13. COVID-19 positive patients required prolonged hospitalization periods compared to non-COVID cases generating a primary driver for additional costs. This prolongation was observed in both mothers and neonates, the latter often requiring specialized neonatal care due to preterm delivery or other complications associated with maternal COVID-19 infection.
14. Therapeutic protocols for COVID-19-positive pregnant women have included the administration of antivirals, immunomodulators, corticosteroids, and anticoagulants in addition to antibiotic, antipyretic, and hydroelectrolyte rebalancing therapy. These drugs, often used for the management of moderate and severe symptoms, but also for the prevention of complications, significantly increased total drug costs.
15. Diagnostic protocols for COVID-19 positive patients were more complex and comprehensive, involving a wider range of laboratory tests and paraclinical investigations. In addition, the need to monitor the health of the mother and fetus meant that these tests had to be repeated, contributing to increased healthcare costs.
16. The need for increased protective measures, including the use of protective suits, FFP2 and FFP3 masks, and other sanitary materials, has led to an even greater increase in costs. These measures were essential to ensure the safety of medical staff and to prevent the spread of the virus within the hospital.
17. The study found that in severe cases of COVID-19 the costs were 80% higher compared to mild cases and 140% higher compared to non-COVID patients. This disparity underscores the financial impact of case severity on medical resources, highlighting the need for efficient resource allocation and management.

As a future recommendation for the first study, it remains for healthcare providers to consider the potential impact of COVID-19 on the course of pregnancy and be prepared to use interventions such as cesarean delivery to optimize maternal and fetal health. In addition, further research is recommended to explore the mechanisms underlying the observed inflammatory responses and to identify strategies to mitigate these risks.

To improve future outcomes, it would be appropriate to implement stricter monitoring protocols for pregnant women diagnosed with COVID-19, especially those with severe

symptoms, and of course to conduct further research to understand the mechanisms underlying the placental changes observed in these cases. Public health guidelines should be updated to reflect the risks associated with SARS-CoV-2 infection in pregnancy, particularly in terms of placental health and the risk of preterm birth.

After the overview of the financial implications faced by healthcare facilities during the COVID-19 pandemic, we can suggest some practical steps to lessen these challenges in the future such as implementing effective resource management strategies, regularly reviewing and updating treatment protocols based on the latest clinical evidence to ensure cost-effectiveness, and increasing investment in preventive measures, including vaccination and public health education, to reduce the incidence of severe cases of COVID-19.

8.2. Personal contributions

Within this thesis:

1. We demonstrated that while the overall rate of preterm births did not significantly increase among SARS-CoV-2 positive pregnancies, there was a notable increase in the incidence of iatrogenic preterm cesarean deliveries. This highlights the critical role of clinical management in the response to COVID-19-related complications during pregnancy.

2. We identified that the severity of COVID-19 symptoms in pregnant women was correlated with a higher likelihood of preterm delivery by cesarean section, highlighting the need for vigilant monitoring and timely medical interventions to optimize maternal and fetal outcomes.

3. Significant placental abnormalities have been shown in COVID-19 positive pregnancies, including reduced placental weight, increased incidence of infarcts, fibrinoid deposits, decidual arteriopathy, intervillous thrombi, and chorangiosis. These findings contribute to our understanding of how SARS-CoV-2 infection affects placental health and function.

4. The association between these placental changes and maternal vascular malperfusion has been emphasized, particularly in severe cases of COVID-19. This emphasizes the potential for compromised placental function to contribute to adverse pregnancy outcomes such as preterm delivery.

5. The financial impact of managing COVID-19 positive pregnancies in a specialized maternity hospital was quantified, demonstrating a significant increase in costs

associated with prolonged hospitalization, specialized medications, comprehensive testing, and enhanced safeguards.

6. It was demonstrated that severe forms of COVID-19 resulted in substantially higher costs compared to mild forms and negative COVID-19 burdens, illustrating the economic pressure of the pandemic on healthcare facilities.

8.3. Future research directions

1. Conduct longitudinal studies to follow the long-term health consequences for babies born to COVID-19 positive mothers, especially those born prematurely or with significant placental abnormalities.

2. To investigate the long-term health effects on mothers who were affected by severe COVID-19 during pregnancy, including the potential impact on subsequent pregnancies.

3. Exploring the molecular and cellular mechanisms underlying the placental abnormalities observed in COVID-19 positive pregnancies. This could involve investigating the direct effects of SARS-CoV-2 on placental cells and the inflammatory responses triggered by infection.

4. Study potential interactions between SARS-CoV-2 and other factors affecting placental health, such as pre-existing maternal conditions and co-infections.

5. Conduct comparative studies to assess the economic impact of COVID-19 on maternity facilities in different regions and health systems. This could help identify best practices and cost-effective strategies for managing pandemic challenges.

6. Assess the cost-effectiveness of different measures implemented during the pandemic to facilitate future resource allocation and policy decisions.

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