UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA" BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

THE IMPACT OF RNA VIRUSES ON PREGNANCY AND MATERNAL-FETAL OUTCOMES

PHD THESIS SUMMARY

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INTRODUCTION

Although there are historical records of possible viral infections (for example, Thucydides described the symptoms of such an infection during the Peloponnesian War), the concept of contagious microorganisms was developed in the 19th century by Louis Pasteur and Robert Koch.

Viruses are essential for understanding human health due to their role in triggering diseases and contributing to medical and environmental solutions.

Viruses are non-cellular entities ranging in size from 20 to 300 nanometers, consisting of nucleic acid (DNA or RNA) in a protein capsid/envelope or a lipid envelope. Viruses can be classified into lipid-enveloped viruses derived from the host membrane and non-enveloped viruses with a protein capsid. Viral replication is driven by genetic material, with auxiliary proteins facilitating this process. Their mechanisms include inhibiting host protein synthesis (modifying normal cell functions to promote their own replication and spread at the expense of host health) and interfering with interferon signaling (increasing the expression of genes that inhibit viral replication and activate immune cells to fight infection). Some RNA viruses, unlike DNA viruses (which can have latency periods), replicate in the cytoplasm and have lower stability, hence a higher mutation rate, with new virus variants emerging more quickly. Given their lifecycle and high mutation rate (which allows them to cause severe infections and evade immune responses), RNA viruses are often involved in epidemics and pandemics and pose a higher risk for pregnant women and fetuses.

For replication, they rely on host cells, with DNA viruses often using the host's cellular mechanism and RNA viruses sometimes encoding their own replication enzymes. Viral pathogenesis involves cytopathic effects, immune responses, and disruptions of host homeostasis.

Prevention and treatment largely rely on vaccines and, to a lesser extent, antiviral drugs. Vaccines are the most effective method for controlling viral infections, although some viruses remain challenging due to high mutation rates and variability. mRNA-based vaccines represent a significant innovation in preventing and/or combating viral diseases, demonstrating high efficacy and the ability to quickly adapt to new viral strains. Understanding the structure and function of viruses that have enabled the development of these vaccines is related to the use of genomic and proteomic sequencing technologies.

GENERAL PART

Chapter 1: The importance of studying the impact of RNA viruses on pregnancy. Relevance of prediction factors for unfavorable maternal-fetal outcomes

Studying the impact of RNA virus infections on pregnancy provides information regarding maternal health and safety, fetal development for adapting medical conduct, creating evidence-based medical guidelines, developing vaccination strategies, personalizing treatments, identifying long-term health implications, shaping public health policies so that rigid general measures are replaced with more flexible ones that prioritize the patient, formulating emergency healthcare regulations and protocols considering the needs of future mothers, whether medical or emotional, managing additional stress and anxiety for pregnant women, providing appropriate support to reduce stigmatization, etc. [1] [2] [3] [4] [5] [6] [7] [8] [9]

Chapter 2: The impact of SARS-CoV-2 on pregnancy and maternal-fetal outcomes

2.1. COVID-19 in the context of physiological, immunological, and endocrine changes in pregnancy

2.1.1. Physiological changes

To meet the metabolic needs of the fetus, protect and develop the pregnancy, and prepare the mother's body for birth and lactation, a series of physiological changes occur, some exposing pregnant women to infections.

2.1.2. Immune system changes

Specific immunological adaptations of pregnancy and physiological changes can amplify the severity of certain respiratory viral diseases such as severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) [10], affecting both maternal and fetal health in the short and long term. Blood tests show that most pregnant patients infected with SARS-CoV-2 exhibit an increase in various inflammatory markers. . [11]

2.1.3. Hormonal changes

SARS-CoV-2 can take advantage of the immunological context generated by hormonal changes occurring during pregnancy.

During pregnancy, levels of estrogens, progesterone, human chorionic gonadotropin (hCG), relaxin, prolactin, cortisol, oxytocin, and thyroid hormones increase to support blastocyst implantation, increase blood flow to reproductive organs, regulate metabolism, provide support for placental development, ensure normal development of fetal organs, prevent uterine contractility during pregnancy, develop mammary glands for lactation, relax ligaments and prepare the body for birth, stimulate uterine contractions during labor, etc.

Statistically, pregnancy does not increase the risk of SARS-CoV-2 infection but increases the incidence of severe forms of the disease. [16] [17]

2.2. Vertical transplacental transmission and placental abnormalities. Maternal-fetal complications

2.2.1. Transplacental transmission

Initial studies excluded the possibility of vertical transplacental transmission due to the lack of cases. Subsequent studies presented cases of newborns with high levels of IgM antibodies that could only have originated from the mother.

2.2.2. Placental abnormalities

SARS-CoV-2 infection has been widely studied, finding that it causes significant pathological changes in the placenta, such as placental infiltration, thromboembolic complications, inflammation and vascular degradation, necrosis, and ischemia, posing potential risks and implications for fetal growth and optimal development, even leading to neonatal death.

2.2.3. Maternal-fetal complications

- maternal complications: severe respiratory infection, acute respiratory failure, preeclampsia and eclampsia, thromboembolism, postpartum hemorrhage, gestational hypertension, the necessity of fetal extraction by cesarean section, spontaneous abortion, admission to intensive care, mechanical ventilation, death, etc.

- fetal complications: intrauterine growth restriction, premature birth, neonatal infection, neurological complications and abnormal development, acute fetal distress, and neonatal sepsis. [56] [57] [58] [59] [60] [61] [62] [63] [64]

2.3. Demographic parameters as predictors of unfavorable maternal outcomes or unfavorable fetal prognosis

- maternal age and gestational age: maternal age over 35 years is predictive due to the increased probability of obstetric complications *(e.g., preeclampsia, premature birth)* amplified by SARS-CoV-2 infection, reduced immune response efficiency, and associated comorbidities.

- socio-demographic status, ethnicity and race, access to prenatal care, compliance, urban vs. rural status, marital status, occupation, vaccination

2.4. Clinical parameters as predictors of unfavorable maternal outcomes or unfavorable fetal

The main clinical parameters, identified anamnestically, subjectively or objectively, by the evaluating medical staff [79] [80] [81] [82]: general condition, vital signs, clinical symptoms, lack of vaccination, severity of COVID-19 infection, blood group, immunosuppression, pre-existing comorbidities - obesity, thrombosis and coagulopathy, hypothyroidism, diabetes, bacterial infections, hypertension, cardiovascular diseases, asthma, and other respiratory conditions.

2.5. Paraclinical parameters as predictors of unfavorable maternal outcomes or unfavorable fetal prognosis

For pregnant women infected with SARS-CoV-2, relevant paraclinical parameters include:

a) laboratory tests:

-sFlt-1 (soluble fms-like tyrosine kinase), complete blood count, Inflammatory profile, D-dimers, transaminases (AST and ALT), coagulation profile, hemoglobin and hematocrit, ferritin, urea and creatinine

b) medical Imaging:

- chest X-ray or thoracic CT, obstetric ultrasound

2.6. Obstetric parameters as predictors of unfavorable maternal outcomes or unfavorable fetal prognosis

a) obstetric complications: gestational hypertension and preeclampsia, preterm labor, premature rupture of membranes, gestational diabetes

b) obstetric history: multiparity, induced abortion, placental disorders

2.7. Fetal parameters as predictors of unfavorable maternal outcomes or unfavorable fetal prognosis

-low birth weight, Apgar score at 1 minute, vertical transplacental transmission, fetal growth rate, oligohydramnios or polyhydramnios, blood flow changes, fetal heart rate *(generally biophysical profile)*, structurally detectable anomalies on ultrasound

2.8. Therapeutic management parameters as predictors of unfavorable maternal outcomes or unfavorable fetal prognosis

-administration of antivirals, administration of corticosteroids, administration of albumin and diuretics

Chapter 3: The impact of HCV on pregnancy and maternal-fetal outcomes

3.1. Negative effects of HCV on maternal-fetal outcomes

Pregnancy in the context of hepatitis C virus (HCV) infection is associated with several maternal complications (gestational diabetes, preeclampsia, preterm birth, intrauterine growth restriction, postpartum hemorrhage, intrahepatic cholestasis, vertical transplacental transmission facilitated by high maternal viral load, HIV co-infection, and premature rupture of membranes) and fetal complications (low birth weight, neonatal infection, developmental anomalies, frequent admissions to the neonatal intensive care unit) due to hepatic inflammation, impaired liver function

and glucose metabolism, metabolic stress, and affected blood flow and nutrient transport to the fetus. [168] [169] [170] [171] [172] [173] [174] [175] [176]

3.2. Prediction factors: demographic, clinical, paraclinical, obstetrical, and fetal factors concerning an unfavorable maternal outcome or an unfavorable fetal prognosis

- **demographic factors**: advanced maternal age, low socioeconomic status, marital status, education level
- **clinical factors**: co-infection with other viruses, pre-existing comorbidities, severe liver fibrosis or cirrhosis
- **paraclinical factors**: elevated serum transaminases, high HCV viral load, serological markers of liver failure
- **obstetric factors**: history of spontaneous abortions, preterm birth, obstetric complications in previous pregnancies
- **fetal factors**: intrauterine growth restriction, prematurity, congenital anomalies associated with HCV infection

Chapter 4: The Impact of HIV on Pregnancy and Maternal-Fetal Outcomes

4.1. Negative Effects of HIV on the Pregnant Woman and Fetus

HIV infection leads to an accelerated progression of the disease in pregnant women, and in the absence of antiretroviral treatment, exposes them to an increased risk of obstetric complications (e.g., preterm labor, premature rupture of membranes, preeclampsia) and opportunistic infections (as a consequence of immune system compromise). Vertical transmission can occur during pregnancy, childbirth, or breastfeeding, with the transmission rate being drastically reduced with appropriate treatment. This exposes the HIV-infected fetus to a risk of neurological disorders and developmental delays. Administering antiretroviral treatment, early interventions, and adapted medical management (avoiding breastfeeding, managing obstetric complications, choosing the method of delivery) are essential to reduce the impact of HIV on pregnancy as well as on maternal-fetal outcomes.

4.2. Prediction Factors: Demographic, Clinical, Paraclinical, Obstetrical, and Fetal Factors Regarding Unfavorable Maternal Evolution or Unfavorable Fetal Prognosis in HIV Infection

- **relevant demographic factors:** a) maternal age, b) socioeconomic status, c) rural vs. urban environment, d) use of antiretroviral therapy,

- **important clinical factors:** a) pre-existing comorbidities, b) obstetric history,

- **paraclinical factors:** a) laboratory tests: values of hemoglobin, leukocytes, transaminases, bilirubin, C-reactive protein, urea and creatinine, maternal anemia, the ratio of CD4+ and CD8+ T cells, high viral load; b) fetal ultrasound: anomalies identified via ultrasound

-obstetrical factors: a) obstetric complications, b) mode of delivery, c) renal or hepatic dysfunction, d) coagulation disorders, etc.

-fetal factors: a) low birth weight and prematurity, b) structural anomalies and congenital malformations, c) intrauterine growth restriction, d) congenital infections, e) cardiac rhythm disorders, f) vertical transmission of HIV

SPECIAL PART (Personal Contributions)

Chapter 5: Working hypothesis and objectives

The present work, "The Impact of RNA Viruses on Pregnancy and Maternal-Fetal Outcomes," aims to evaluate the maternal-fetal complications associated with viral infections: SARS-CoV-2, Hepatitis C Virus, and HIV. The thesis is structured into two research directions and aims to establish correlations between the demographic, clinical, and paraclinical aspects of pregnant women with viral infections and fetal prognosis.

A. The first research direction aimed to determine the clinical and paraclinical particularities of the studied groups. It also included a comparative analysis using clinical, demographic, obstetrical, and fetal parameters between the group of patients with RNA viral infections and the group of patients without RNA viral infections.

B. The second research direction focused on patients with SARS-CoV-2 infection, investigating the existence of predictors associated with unfavorable maternal-fetal outcomes.

The study objectives can be approached as follows:

1. establishing a demographic profile of pregnant women with RNA viral infections
2. identifying maternal factors that may lead to an unfavorable pregnancy prognosis
3. establishing various correlations between risk variables
4. identifying paraclinical parameters associated with unfavorable maternal outcomes
5. identifying maternal paraclinical parameters associated with unfavorable fetal prognosis

Source of data: The Information System of the University Emergency Hospital Bucharest, patient observation sheets, neonatal records, and personal medical records.

Chapter 6: General research methodology

A. Methodology:

1.Type of epidemiological study

-descriptive and analytical due to the monitoring of risk factors influencing maternal-fetal prognosis.

2. Sources and methods of data collection:

-medical information was extracted from observation sheets and the InfoWorld information system of the University Emergency Hospital Bucharest, Obstetrics-Gynecology Clinic. Data were also collected from patients' medical records when pregnancies were monitored.

3. Sample volume determination:

-the study was conducted on a sample of 179 pregnant women with RNA viral infections (SARS-CoV-2, HCV, HIV) and a control group of 97 pregnant women without viral infections who gave birth at the University Emergency Hospital Bucharest between January 1, 2020, and December 31, 2023.

Inclusion criteria:

- Pregnant women over 18 years old known or newly diagnosed through peripartum screening with HCV, HIV, or SARS-CoV-2 infection;
- Delivery at the Obstetrics-Gynecology Clinic, University Emergency Hospital Bucharest;

- Signed informed consent according to the local ethics committee's approval.

Exclusion criteria:

- Non-compliance with study objectives and refusal to participate.

Ethical principles:

- The study was conducted with the approval of the Ethics Committee of the University Emergency Hospital Bucharest (No. 58134/16.11.2020).

B. Methods:

1. Measurement and analysis of variables

- statistical data processing using R version 4.4.0 and graphical representation using both R and Microsoft Excel 2019. Data analysis, coding, and application of statistical tests were reported according to the variable typology.

2. Graphical representation of variables:

- Box plot diagrams
- Bar charts
- Effect plots diagrams

3. Statistical methods:

- Two-tailed Welch T-tests
- Pearson chi-square tests
- Fisher's exact tests
- Simple univariate binomial logistic regression with probit link function
- Univariate Poisson regression

Chapter 7: Results

A total of 276 cases of deliveries at the University Emergency Hospital Bucharest between January 1, 2020, and December 31, 2023, were analyzed in the thesis.

7.1. First research direction:

The first research direction aimed to compare the two study groups *(group A with RNA viral infections and group B, the control group)* concerning demographic, clinical, paraclinical, obstetric, and fetal parameters *(IUGR, birth weight, Apgar score at 1 minute).*

Demographic parameters

- the age of pregnant women with RNA viral infections was on average lower than that of patients in the control group (29.97 ± 6.25 vs. 31.65 ± 5.55), with a statistically significant result (p=0.024).

- for the HIV-positive patients, the low number of registered cases only allowed for an analysis of continuous variables.

- the average age of HIV-positive patients was 29.89 ± 5.53 years;

- 66.67% of HIV cases were unmonitored pregnancies (6 cases), with 22.22% resulting in preterm births;

- in the HCV-infected group, the percentage of unmonitored pregnancies was significantly higher at 80.95%.

Clinical parameters:

I. SARS-CoV-2 infection:

- for SARS-CoV-2 infected patients with bacterial infections, the average hospitalization days were 5.45 ± 5.43, ranging from 2 to 29 days.

- for SARS-CoV-2 infected patients without bacterial infections, the average hospitalization days were 4.47 ± 3.94.

- for SARS-CoV-2 infected patients requiring ICU admission, the average hospitalization days in group A were 15.38 ± 9.69, while in the control group, the average was 9.75 ± 4.92 days.

Paraclinical parameters:

I. SARS-CoV-2 infection

- the average platelet count in pregnant women with viral infections was 226.77 ± 73.77 10*3/uL, significantly higher than in the control group (200.54 ± 74.02 10*3/uL).

- a statistically significant relationship was observed between the APTT value in group A (30.01 ± 4.05%) and the APTT value in group B (28.05 ± 2.88%).

- the INR value was slightly higher in the viral infection group compared to the control group (1.04 ± 0.65 vs. 0.98 ± 0.07).

- in the comparative analysis of pregnant women with hypertensive pregnancy complications in the two groups, the average ALT value was significantly higher in the viral infection group compared to the control group (65.9 ± 85.73 U/L vs. 41.15 ± 63.53 U/L).

II. HIV infection:

- a direct proportional relationship was observed between hemoglobin, hematocrit, leukocytes, basophils, and eosinophils values and maternal and fetal values.

III. HCV infection:

- in the HCV-infected group, associated urogenital infections were present in 52.38% of cases.

Obstetric parameters:

I. HIV infection:

- in 77.78% of HIV cases, the mode of delivery was cesarean section, with the following indications:

- Prophylaxis of vertical HIV transmission - 3 cases (42.86%)
- Imminent uterine rupture - 3 cases (42.86%)
- Placenta previa with significant bleeding - 1 case (14.28%)

II. HCV infection:

-the mode of delivery was cesarean section in 66.67% of cases, with the following indications:

- Prophylaxis of vertical transmission - 21.43%
- Imminent uterine rupture - 42.86%
- Placenta previa with bleeding - 14.28%
- Acute fetal distress - 21.43%

Fetal parameters:

I. HIV infection:

- the average birth weight was 2900 ± 508.63 grams;
- intrauterine growth restriction was recorded in 22.22% of cases;
- the average Apgar score at 1 minute was 7.89 ± 1.36.

II. HCV infection:

- the average fetal weight was 2455.71 ± 661.28 grams;
- the average Apgar score at 1 minute was 7.71 ± 1.1.
- of the newborns with an Apgar score at 1 minute less than or equal to 7, 85.71% required therapeutic management in the Neonatal Intensive Care Unit.

7.2. Second research direction:

The second research direction targeted patients with COVID-19 infection, aiming to determine predictors associated with unfavorable maternal and fetal prognosis.

- a statistically significant relationship was observed between the absence of antenatal monitoring of SARS-CoV-2 infected pregnant women and the risk of requiring therapeutic management in the ICU (p=0.048).
- older gestational age was associated with a lower risk of ICU admission; each additional week of gestational age reduced the risk of ICU admission by 12%.
- unmonitored pregnancies had a 2 times higher risk of ICU admission.
- higher hemoglobin levels were associated with a lower risk of ICU admission; each 1 g increase in hemoglobin reduced the risk of ICU admission by 34%.
- higher hematocrit levels were associated with a lower risk of ICU admission; each 1% increase in hematocrit reduced the risk of ICU admission by 12%.
- pregnant women who were not administered Remdesivir had a nearly 10 times lower risk of ICU admission.
- pregnant women who were not administered corticosteroids had a nearly 4 times lower risk of ICU admission.
- a statistically significant relationship was observed between the hospitalization period and maternal age (p=0.014) as well as between the hospitalization period and the patient's environment (p=0.018).
- each additional week of gestational age was associated with a 12% reduction in hospitalization days.
- associated bacterial infections led to an extension of the hospitalization period (p=0.019). Thus, their absence was associated with an 18% reduction in hospitalization days.
- unmonitored pregnancies were associated with a 17% increase in hospitalization days, with statistical significance (p=0.047).
- a 33% reduction in hospitalization days for SARS-CoV-2 infected pregnant women who delivered naturally compared to those who delivered by cesarean section.
- an increase in serum hemoglobin by 1 g was associated with an 18% reduction in hospitalization days.

- an increase in hematocrit by 1% was associated with a 7% reduction in hospitalization days.
- an increase in serum creatinine by 0.1 mg/dL was associated with a 45% increase in hospitalization days.
- pregnant women who were not administered Remdesivir had an average hospitalization period nearly 3 times shorter.
- in patients who did not require anticoagulant administration, the average hospitalization period was 36% shorter.
- in patients who were not administered corticosteroids, the average hospitalization period was approximately 50% shorter.
- each additional week of gestational age reduced the odds of ICU admission by 42%.
- a statistically significant relationship was observed between maternal hemoglobin levels ($p=0.032$) and liver function parameters.
- higher maternal ALT levels were associated with higher odds of neonatal ICU admission.
- a statistically significant relationship was observed between Remdesivir administration and neonatal ICU admission probability ($p=0.004$) as well as between diuretic administration and fetal prognosis ($p=0.007$).
- pregnant women who did not undergo Remdesivir therapy had a 5 times lower risk of neonatal ICU admission.
- intrauterine growth restriction and Apgar score at 1 minute were statistically significant predictors of neonatal ICU admission, with a nearly 10 times higher probability.

Chapter 8: Discussions

RNA viral infections associated with pregnancy represent a significant public health issue given the high rate of maternal-fetal complications. The research data can be correlated with those from other studies in the literature.

Regarding SARS-CoV-2 infection:

- pregnancy can be associated with a high risk of developing maternal complications due to adaptive physiological changes involving the immune, respiratory, cardiovascular, and metabolic systems.
- it is associated maternally with a higher risk of preeclampsia or gestational diabetes and a higher rate of cesarean delivery.
- the risk of ICU admission or maternal death is high, although the incidence of SARS-CoV-2 infection is comparable between pregnant patients and the general population.
- fetal prognosis is affected by a higher risk of intrauterine growth restriction, preterm birth, or even intrauterine fetal death.
- viral infections, including SARS-CoV-2 infection, can lead to potential exacerbation of autoimmune pathologies that, in turn, are associated with increased maternal-fetal morbidity and mortality.

Regarding HCV infection associated with pregnancy:

- patients with HCV-induced cirrhosis experience maternal complications such as preeclampsia, increased risk of bleeding, cesarean delivery, or maternal death.
- regarding fetal prognosis, the risks of preterm birth, growth restriction, or fetal death are exponentially high.

HIV infection:

- it is associated with increased fetal mortality and morbidity, especially in cases with high viremia and the absence of antiretroviral treatment.
- the risk of preterm birth, intrauterine growth restriction, and intrauterine fetal death increases in pregnancies associated with HIV infection.

Chapter 9: Conclusions and personal contributions

9.1. Conclusions

At the beginning of 2020, European countries reported the first cases of maternal-fetal transmission of COVID-19. The pandemic raised concerns, including the impact of SARS-CoV-2 infection on pregnant women. A significant effort was mobilized to discover useful vaccines and treatments and to clarify through initiated studies any imaginable aspect that could ease the healthcare burden, optimize medical outcomes, and reduce maternal-fetal mortality and morbidity. To join this effort, we initiated research on the impact of RNA viral infections on pregnancy and implicitly on maternal-fetal prognosis, leveraging the experience of the University Emergency Hospital Bucharest within the limits of collected data. To achieve the research objectives, a comprehensive database was created to provide information necessary for statistical analysis. The research illustrated the importance of identifying and managing specific risk factors such as comorbidities and monitoring hematological parameters with predictive value for severe complications to implement preventive medical measures ensuring favorable prognosis for both mother and fetus. Equally, the research emphasizes the essential nature of regular and comprehensive antenatal care, which can drastically reduce ICU admission risk, and the correlation between anticoagulant administration and comorbidity management on one hand and hospitalization days on the other. Lastly, the research reinforced the idea that SARS-CoV-2 infection does not increase the risk of intrauterine fetal death and that the presented data on infection prevalence and incidence allow for targeted resource allocation decisions.

LIST OF PUBLISHED SCIENTIFIC WORKS

Articles published in medical journals:

1. IORDACHE, M., DUMITRU, A., TURCAN, N., & CIRSTOIU, M. M., „Sonographic Signs of SARS-CoV-2, Placentitis. Association with Pregnancy Outcome" *A Journal of Clinical Medicine, ,* 2024:19(2)
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   Chapter 7, subsection 7.2, pages 90-93

2. IORDACHE M, MECA D, CIRSTOIU M, „SARS-CoV-2 Infection in Pregnant Women With Hypothyroidism" *Cureus ,* (May 27, 2024),16(5): e61206.
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3. IORDACHE MD, MECA DC, CIRSTOIU MM., „Fetal Clinical and Paraclinical Outcomes in HIV-Positive Pregnant Women" *Cureus,* 2024 May 3;16(5).
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