Unfavourable outcomes of pregnancies in KBC Split in the year 2019 and 2020 in regard to COVID-19 pandemic

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Diploma thesis

Academic year:
2021/2022

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My Omar's are truly everything I need in life.

LIST OF ABBREVIATIONS

ACE2 – Angiotension Converting enzyme 2

ACOG - American College of Obstetricians and Gynecologists ACOG

APLS - Antiphospholipid antibody syndrome

aPPT - Activated partial thromboplastin time

ARDS – Acute respiratory distress syndrome

COVID-19 – Coronavirus disease 19

CRP – C-reacitve protein level

ESR – Erythrocyte sedimentation rate

ICTV – International Committee on Taxonomy of Viruses

ICU – Intensive Care Unit

MERS-CoV - Middle East respiratory syndrome coronavirus

PROM – Premature rupture of membrane

PT – Prothrombin time

ReCoDe – Relevant Dondition of Death

SARS-CoV-2 – Severe Acute Respiratory Syndrome coronavirus 2

WHO – World Health Organization

1. INTRODUCTION

1.1. Coronavirus disease 19

Coronavirus disease, also known as COVID-19, is an acute infectious disease caused by the Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2 virus). It was first discovered in Wuhan, China, December 2019 (1). At first, it was described as the novel coronavirus "2019-n-CoV" by World Health Organization (WHO), but due to its resemblance with the previous SARS-CoV virus the International Committee on Taxonomy of Viruses (ICTV) decided to term it severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This viral outbreak was declared as a public health emergency of international concerns by WHO on the 30th of January 2020. The viral infection started to spread widely and rapidly and on the 11th of March 2020, WHO declare COVID-19 as a global pandemic (2).
By 22nd of May 2022, there were more than 518 million cases reported worldwide and over 6 million deaths have been confirmed (3).

Clinical epidemiologist suggests that the initial transmission from bats to human is linked to the Huanan Seafood Wholesale Market, even though the route of transmission was not well established (4,5). As of today over 200 countries have reported COVID-19 positive cases (6).

The first reported case of a positive COVID-19 patient in Croatia was on the 20th of February 2020 (7). As shown in figure 1, Croatia reached a peak in newly diagnosed patients at four different occasions, with the latest one taking place in January 2022. So far, Croatia had over 1.1 million confirmed cases of COVID-19 with over 15.000 deaths, meanwhile Split-Dalmatian County had over 150 thousand cases with 1.300 deaths (8).

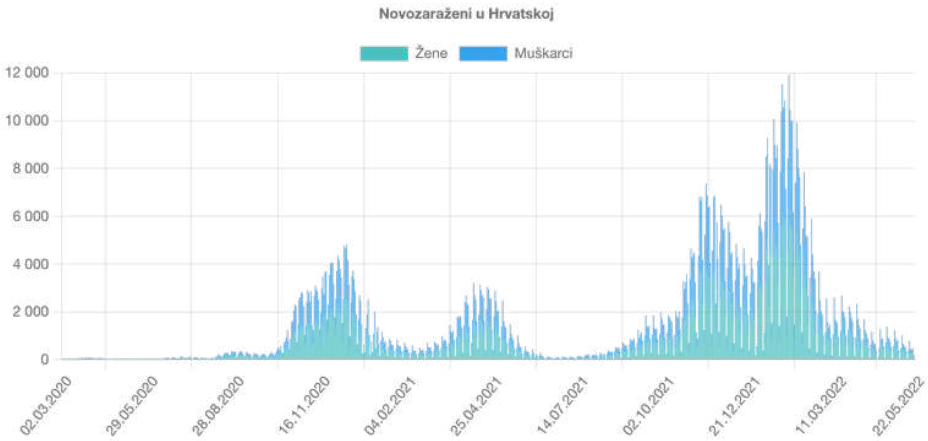

Figure 1. Cases of COVID-19 in Croatia from 02.03.2020 to 22.05.2022 (9).

1.1.1. Etiology of COVID-19

Coronaviruses constitute a viral envelope, with a positive-sense single-stranded RNA genome. Based on their different genomic structure they can be divided into four genera; α, β, γ, and δ, with the potential to infect various host species. α and β are responsible for infecting mammals. SARS-CoV-2, together with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) are classified as β coronaviruses (10).

1.1.2. Etiopathogenesis

It is now widely known that coronavirus spreads through respiratory droplets via close person-to-person contact with an infected individual. Respiratory droplets are formed when an individual with an ongoing corona infection speaks, sneeze or coughs, these travel short distances before they land on a mucosal surface and further spread the virus. Aerosol transmission has also been established, which can travel a longer distance of > 6 feet and thereby transmit the virus in a non-contact manner, however this occurs less commonly. Another way of transmission is trough contact with a contaminated surface. It is difficult to control the spread since both symptomatic, pre-symptomatic and asymptomatic individuals can be carriers of the virus and thereby transmit it. Patients are most contagious days before and after the onset of symptoms, meaning that the risk of transmission is directly related to viral load (11).

The viral life cycle begins with attachment to the host cell, penetration then takes place via membrane fusion or endocytosis. Viral RNA enters nucleus where viral proteins are produced trough viral mRNA, this process is defined as biosynthesis. New viral particles are then matured and released.(10) 29 viral proteins have been identified so far, however nucleocapsid (N), envelope (E), spike (S) and membrane (M) proteins, are by far the most important ones (12). Spike proteins, which are made up of two subunits and distributed throughout the viral surface, are the principal proteins for host entry. Subunit S1 binds to receptor of host cell and subunit S2 is responsible for cellular membrane and viral fusion. SARS-CoV-2 enter the host cell by S proteins binding to receptors on host cell, namely Angiotensin Converting enzyme 2 (ACE)2. Spike protein-ACE2 complex is cleaved by a protease leading to exposure of fusion peptides. This triggers membrane fusion and eventually release of viral RNA and viral replication (12,13).

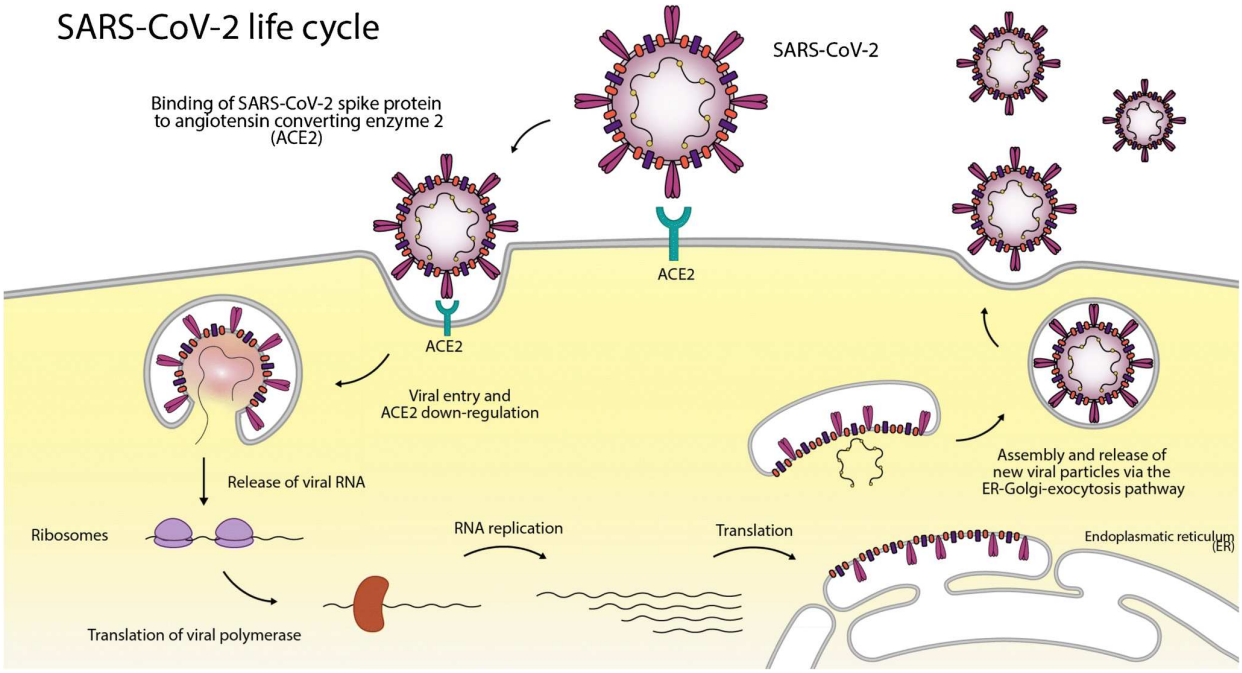

Figure 2. SARS-CoV- life cycle (14).

ACE2 is abundantly expressed in lungs, more specifically in type II alveolar cells and respiratory epithelial cells. It is also detected in myocardial cells, esophageal epithelial cells, endothelial cells and artery smooth muscle cells, uterus epithelial cells, ovarian cells, and lastly in cells of the colon (14).

1.1.3. Clinical manifestations

COVID-19 has a wide range of symptoms with varying degree of severity, it affects different organ systems, primarily respiratory system, and usually has a gradual onset of symptoms. Clinical manifestation ranges from asymptomatic patients or those with only mild influenza-like symptoms such as: mild fever and fatigue, rhinorrhea, sore throat and/or conjunctivitis on one side of the spectra. On the other side of the spectra patient might experience sever, life-threatening complications such as acute respiratory distress syndrome (ARDS), organ failure, or shock, that subsequently can lead to death of the patient (15). This is particularly noted in elderly and immunocompromised individuals (16,17).

Fever is the most common symptom and occurs in up to 98% of patients. Other frequent symptoms are cough, fatigue, shortness of breath and muscle soreness seen in up to 82%, 44%, 55% and 44%, respectively (15). Other important symptoms that have been recognized and

reported among patients suffering of COVID-19, are neurological disturbance including hyposmia, anosmia, parosmia and dysgeusia, indicating a chemosensory disturbance. Even though COVID-19 primarily is a respiratory disease, various extrapulmonary manifestations can occur. In patients treated for an ongoing COVID-19 infection in ICU up to 30% were complicated by a thromboembolic event, such as thrombosis and myocardial infarction. Cardiovascular manifestations have also been reported, leading to direct or indirect cardiovascular injuries; cardiomyopathies, cardiac arrythmias, acute coronary syndrome and cardiogenic shock. Hematuria and proteinuria are signs of acute kidney injury, which is seen in up to 37% of hospitalized patients. Additional symptoms such as anorexia, diarrhea, nausea, vomiting, and abdominal pain are gastrointestinal symptoms associated with prolonged COVID-19 infection. Increased bilirubin and eventually liver injury might also be a consequence of COVID-19 infection. Neurological manifestations have already been mentioned; however headache and dizziness have also been reported in milder cases. Confusion or impaired consciousness, acute stroke, Guillain-Barré syndrome and meningoencephalitis are some of the more severe neurological manifestations (15).

The most common laboratory finding in an infected individual is lymphopenia, normal or lower white blood cells counts or thrombocytopenia, accompanied by an increase in CRP (C-reactive protein level). Other inflammatory markers, such as; erythrocyte sedimentation rate (ESR) and procalcitonin are also increased in the acute phase. Increased prothrombin time (PT) in conjunction with prolonged activated partial thromboplastin time (aPTT) has also been reported. Together with these findings D-dimer is further supporting coagulopathy, it is also used to indicate the severity of disease (18). A high suspicion of COVID-19 can be established when a patient presents with upper respiratory tract symptoms, fever, lymphopenia, or leukopenia together with a history of close exposure to the virus or travel to endemic area.

Approximately 80% of SARS-CoV2 infected patients present with mild respiratory tract infection and can thereby be managed with outpatient care. Improvement of symptoms with mild-moderate infection usually occurs at the 10^{th} day counting from the initial symptoms. However, clinical deterioration is also seen around this time and around 15% of patient with moderate-severe pneumonia caused by COVID-19 need inpatient care (15,19).

1.1.4. Complications

Multiple major organs can be involved during COVID-19, leading us to describe it as a systematic viral illness. Several complications have been reported, advanced age, comorbidities

such as diabetes mellitus, obesity, cardiovascular and chronic lung diseases, chronic kidney and liver diseases, and neoplastic conditions are associated with increased risk for complications and severe COVID-19. Male gender is also a contributing factor (20,21). Pulmonary embolism, being the most important coagulopathy, but also others such as deep venous thrombosis, myocardial infarction and ischemic stroke are associated with severe COVID-19 infection. Despite prophylactic therapy, these thromboembolic events still occur with high prevalence (22). In 3% of hospitalized patient, disseminated intravascular disease (DIC) was observed, being reported to be a poor prognostic factor, and connected to severe illness (21). Left ventricular dysfunction, acute pericarditis, cardiomyopathies, arrythmias and cardiogenic shock are cardiovascular complications associated with coronavirus infection (20,21). In critically ill COVID-19 patients GI complications including bowel ischemia, bleeding in gastrointestinal tract, pancreatitis and severe ileus are commonly seen.

The most common extrapulmonary manifestation associated with coronavirus disease 19 disease and higher rate of mortality is acute kidney failure (21). In 30% of patients being treated with intensive mechanical ventilation, ventilation-associated pneumonia develops. Severe disease complicated by acute reparatory distress syndrome (ARDS) is reported in 5% of COVID-19 patients and need hospitalization in intensive care unit. In some cases, it is proceeded by sepsis, septic shock, multiple organ failure and eventually death (20).

1.2. Pregnancy and COVID-19

Since the outbreak of COVID-19 pandemic, many questions have been raised regarding COVID-19 effects on pregnant women. Whether there is an increased susceptibility to SARS-CoV-2 infection and whether there is an increased risk for severe disease. Also, if it leads to any unfavorable outcomes in pregnancy. The risk of vertical transmission of the virus from mother to fetus have also been of great concern (23,24).

Early during the pandemic, no evidence of vertical transmission from mother-to-child of SARS-CoV-2 was reported. However, recent reports show possible in utero transmission (25).

It is already well known that pregnancy leads to both physiological and immunological changes. Pregnant women are at increased risk of immunocompromised state due to alternation in cell immunity and by such means more prone to developing worst outcome compared to non-pregnant women. Physiological changes are most pronounced in the respiratory systems such as elevation of diaphragm, hyperventilation due to increase in pulmonary pressure, reduced

functional residual volumes and respiratory failure because of hypoxic event. Additionally, increase in demands for both maternal and fetal oxygen and gestational anemia all increase the probability of physical dyspnea, which is seen in the third trimester, thereby contributing to even further breathing difficulties (26).

Research shows conflicting results regarding susceptibility and severity of disease in pregnant women, where on one side no increase susceptibility or severer disease has been reported and on the other side there is a clear increased risk for both susceptibility and a more severe course of disease.

One study that was conducted reported that despite there being many physiological and immunological factors that potentially could increase the risk of acquiring SARS-CoV-2 infection, as discussed previously, the data published so far do not mirror an increased risk, nor a worse clinical manifestation of pregnant women in comparison to non-pregnant women (23,27,28). In a literature review by Selim *et al.* it was reported that an absolute risk of SARS-CoV-2 infection in pregnancy is considerable very small (28). Another study reported that their exist a higher probability of being infected with COVID-19 during pregnancy, but also that pregnant woman with COVID-19 infection will have a more severe course. The susceptibility for SARS-CoV-2 in pregnant women is correlated with the amount of ACE2 expressed, which is upregulated during pregnancy (23,27).

1.2.1. Symptoms of COVID-19 in pregnant women

The clinical manifestation of COVID-19 in pregnant women are similar like those of non-pregnant women. These include fever (68%) and cough (34%) as most common symptoms, but dyspnea (12%), malaise (12%) and diarrhea (6%) are also often reported (29). Also, the rate of clinical complication of COVID-19 infection in pregnant women are very similar to those in the general population where 81% develop mild symptoms, 14% develop severe complications, and the last 5% go on to the critical stage of disease (26). A large cohort study, conducted by World Health Organization, including 147 COVID-19 positive pregnant women reported that 8% became severely ill and only 1% became critically ill. With this data, it was suggested that pregnant women with COVID-19 infection had milder clinical manifestations (29). Maternal complications are commonly seen in pregnant women infected with SARS-CoV-2. One of the most common outcomes in pregnant women positive for COVID-19 is pneumonia. Most commonly, pregnant women suffer from mild-to-moderate COVID-19 related pneumonia, this was reported by a meta-analysis that included nine publications and 87 SARS-CoV-2 positive

pregnant women, where the clinical manifestations where similar to those seen in adults with COVID-19 pneumonia (23).

The rate of admission to intensive care unit (ICU) of pregnant women with COVID-19 pneumonia have been shown to not differ from that of nonpregnant women. However, higher rates of caesarean section delivery and preterm birth have been reported. In previous corona diseases, more specifically SARS and MERS, fatality rate was between 25-27%, compared to COVID-19 with only 1% fatality rate (29). However, in another study it was reported that there is an increased rate of hospitalization among pregnant women with SARS-CoV-2 infection, as well as increased rate for the use of mechanical ventilation. But there was no affect in mortality rate compared to general population. According to this study, an infected pregnant woman was five times more prone to be admitted to ICU and four times more prone to be treated with mechanical ventilation compared to non-pregnant women (30). However, today's research shows different results. One study showed that the risks of worsening and progressing to the critical stages of the disease, as well as the need for mechanical ventilation, are greater among pregnant women than among the general population (31). Preterm labor, premature rupture of membranes (PROM) and placental abruption are complication of maternal pneumonia that can lead to fetal or maternal death (30).

1.2.2. Pregnancy outcomes during COVID-19 infection

In the initial phase of the COVID-19 pandemic, researchers could not find a difference that was significant enough when comparing women with COVID-19 infection to healthy women in the frequency of fetal distress, preterm labor, and neonatal asphyxia (30).

However, evidence that SARS-CoV-2 have a negative outcome on pregnancies are now starting to pile up, even though vertical transmission from mother-to-fetus rarely appears (24). It has now been reported that pregnant women with confirmed SARS-CoV-2 infection have an increased risk of preterm birth, preeclampsia, and stillbirth. There was also a difference in symptomatic and non-symptomatic COVID-19 positive pregnant women, where an association of increased risk for cesarean delivery, hypertensive disorders, and preterm birth was more associated with symptomatic COVID-19 infection. Gestational diabetes, preeclampsia, low birth weight, and preterm birth has been shown to have a strong association with severe COVID-19 disease, compared to mild disease (24,32).

The association between preeclampsia and COVID-19 infection in pregnant women is still under investigation. However, infection with SARS-CoV-2 has shown to lead to

dysfunctions in renin-angiotensin system as well as vasoconstriction due to angiotensin-converting enzyme 2. Other studies have also shown that COVID-19 positive patients may be accompanied by proinflammatory state that eventually proceed to systemic endothelial dysfunction and preeclampsia. Important to mention is that systematic endothelial dysfunction is also a hallmark of preeclampsia, therefore COVID-19 disease and its vascular events may share a common pathway with preeclampsia (32). A study preformed in Sweden including over 2500 patient also concluded that pregnant women with confirmed COVID-19 had a higher prevalence of preeclampsia (33).

Spontaneous abortion, also called miscarriage, is another unfavorable outcome that has been associated with SARS-CoV-2 infected pregnant women (34,35). This is believed to be due to changes and inflammation of the placenta leading to fetal growth retardation and then induces spontaneous abortion (36). Infection with SARS-CoV-2 during preconception period and during the first half of pregnancy has been associated with an increased risk for both miscarriage and failure of embryo implantation (12).

A large study conducted in the United State in March of 2021 confirmed that there is an increased risk for stillbirth in women with documented COVID-19 infection during the delivery hospitalization. The association was stronger with delta variant of coronavirus 19, delta variant was classified by WHO in May 2022 (37,38). The results of this study showed that 1.171 stillbirths occurred during the Delta variant period (July-September 2021), this accounting for 2.70% of the deliveries in COVID-19 positive pregnant women. Stillbirth occurred in 0.63% of women without documented COVID-19 infection (but in the period of COVID-19 pandemic), when compared with stillbirth rate before the pandemic, with a rate of 0.59% we see that it is quite similar (38).

It is not only the direct impact of COVID-19 that plays a role in pregnancy outcomes, but the healthcare system has also been affected due to the pandemic in various ways, contributing to the adverse effects in pregnant women, also those not infected with SARS-CoV-2. A global systemic review observed an increase rate of stillbirth, decline in maternal mental health, and increase rate of ectopic pregnancy rupture representing a delay in care during the pandemic compared to prior to the pandemic (39).

1.2.3. Treatment of COVID-19 in pregnant patients

General measurements such as early isolation, control of infection, empirical antibiotics, oxygen therapy, mechanical ventilation for respiratory failure, fetal monitoring and multidisciplinary approach is important in management of COVID-19 in pregnant patients (40).

Hydroxychloroquine, ivermectin, and nitazoxanide are anti-viral drugs, decreasing the viral load, that are both safe and effective to use in pregnant women during the initial mild phase of COVID-19 infection. Azithromycin, a broad-spectrum antibiotic, can either be used as a monotherapy or in combination with anti-viral drugs, especially the use of azithromycin together with hydroxychloroquine is proven to be effective. However, the dose of azithromycin is reduced in pregnant women compared to non-pregnant women (41,42).

In moderate and severe cases of COVID-19, the treatment of pregnant patients should not differ from that of non-pregnant patients. Corticosteroids are today considered the most important drugs in COVID-19 infection, however in the beginning of the pandemic, it was thought that the use of corticosteroids may be associated with morbidity and mortality. This was disproven by a study in 2020, that showed the benefits of corticosteroid use in patients with oxygen therapy or mechanical ventilation (43,44)

Both COVID-19 disease and state of pregnancy leads to a hypercoagulable state, with increased risk for deep venous thrombosis and pulmonary embolism (45,46). The use of low molecular weight heparin, such as enoxaparin, is controversial. Some studies showed a benefit of anticoagulant therapy, especially in pregnant women with COVID-19 together with other risk factors such as obesity. On the other hand, other studies reported a 2.3-fold increase mortality leading to the conclusion that anticoagulant therapy might not be beneficial. Other authors claim that thrombosis might have been a contributing factor for mortality, but not appear to be the cause or related to the cause. However, most authors and research papers agree that anticoagulant therapy with enoxaparin is of benefit in critically ill pregnant patients (47,48).

1.3. Unfavorable outcomes in pregnancies

Pregnancy comes with a risk, and all pregnancies will sooner or later end in miscarriage, stillbirth or ideally in a live birth child. Miscarriage is a very frequently outcome of pregnancy and together with intrauterine fetal demise it is associated with an enormous psychological and physical stress for both parents (49). In Croatia during the year 2020, 142 neonatal deaths were

reported, leading to a neonatal mortality rate of 3.9/1000 live births and 5.390 miscarriages were reported (50,51).

1.3.1. Miscarriage

Miscarriage, also called spontaneous abortion, is defined as pregnancy loss before 20 weeks of gestation, where the fetus weights less than 500 grams and is without any vital signs for instance; pulse, respiration, and umbilical cord pulsation (34,52,53). According to American College of Obstetricians and Gynecologists (ACOG) miscarriage is the most common form of pregnancy loss, estimated to occur in 26% of all pregnancies, however some of these take place very early in gestation and might be mistaken for a heavy menstruation. Meanwhile, miscarriages in clinically recognized pregnancies occur in up to 10%. Out of all miscarriages 80% occur in the first trimester (from conception to 12 weeks), and these are termed early pregnancy loss. After gestational week 12, the risk and incidence for miscarriage declines. There are different forms of miscarriage and five types have been identified, namely; threatened-, inevitable-, incomplete-, complete-, and missed abortion (34,53).

The most common risk factors for miscarriage are obstetrical history of a previous miscarriage and advanced maternal age. In women aged 20-30 the incidence for miscarriage is 9-17%, meanwhile it is as high as 80% in women over 45 years (34). Other risk factors include maternal comorbidities such as maternal obesity, antiphospholipid antibody syndrome, and thrombophilia as well as cigarette smoking, alcohol consumption and large amounts of caffein consumption.

Fetal chromosomal abnormalities, most frequent being trisomy followed by polyploidy and monosomy X, are the most common cause of miscarriage and account for approximately half of all miscarriages. Figure 3 shows a congenital anomaly leading to early neonatal death. (34,54).

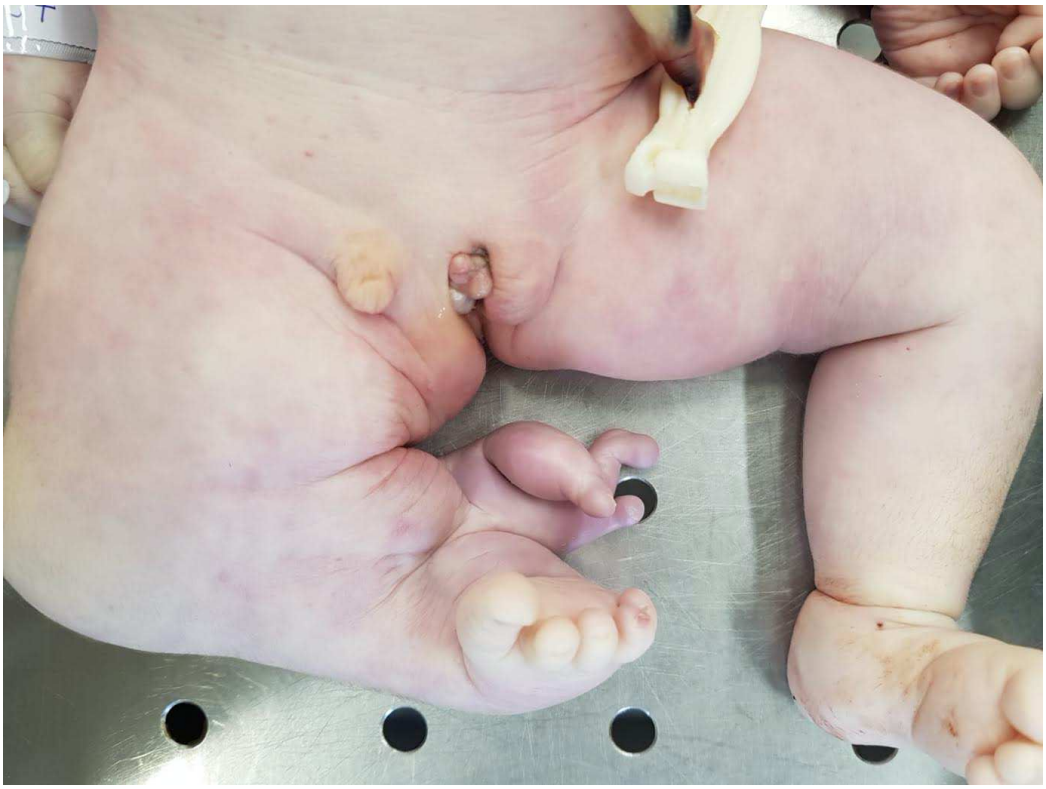

Figure 3. Example of congenital anomaly. Figure demonstrates part of OEIS complex, anomaly of the anogenital region, coupled with lower extremities anomalies.
(Figure is taken from mentor's archive.)

1.3.2. Threatened abortion

The diagnosis of threatened abortion can be presumed with the presence of vaginal bleeding or discharge occurring early in the pregnancy. The cervical os is closed and there is no passage of products of conception, also transvaginal ultrasound shows a viable fetus. Threatened abortion are the most common complications of early pregnancy loss and affects 20-25% of women during early gestation (53,55,56). Approximately 50% progress to abortion, even though the risk is lower if fetal cardiac activity is seen (53,56).

1.3.3. Inevitable abortion

As in threatened abortion, vaginal bleeding also occurs in inevitable abortion, however on pelvic examination the cervical os is open in inevitable abortion. This will cause the passage of fetus or products of conception through cervix. The fetus can be either viable or non-viable on transvaginal ultrasound (54,56).

1.3.4. Incomplete abortion

Incomplete abortion is defined as vaginal bleeding and lower abdominal pain and/or cramping, together with an open cervical os on examination where not all products of conception have been expelled, so called “incomplete passage”. Usually, they cannot be prevented(34,57,58).

1.3.5. Complete abortion

In complete abortion there is vaginal bleeding and complete passage of fetus or products of conception through cervix. When performing transvaginal ultrasound, no remaining’s of conception products can be seen in the uterus (54,56).

1.3.6. Missed abortion

Missed abortion is associated with vaginal bleeding with or without passage of fetus or products of conception. Cervical os should be closed on examination and on transvaginal ultrasound no viable fetus can be seen, however some residual products of conception might be detected (54). In other words, missed abortion is the loss of an embryo or fetus not associated with any uterine contractions (34).

1.3.7. Induced abortion

Women in reproductive age are at risk for unintended pregnancy and thereby might undergo induced abortion which is described as a procedure done intentionally to end a pregnancy. Most induced abortion are performed before the 12th week of gestation (59).

1.3.8. Recurrent miscarriage

Recurrent miscarriage, also known as recurrent pregnancy loss or habitual abortion, is defined as a pregnancy loss before 20 weeks of gestation in three or more consecutive pregnancies (60,61). It is estimates that recurrent miscarriage affects 1% of all women in childbearing age. It is now a common problem and concerns both patients and doctors since it

is not easy to find a clear etiology and thereby also difficult to appropriately treat (55). Some clinicians and researchers define recurrent miscarriage as two or more pregnancy losses which expands the problem from 1% to 5% of conceiving couples (52).

Many factors and etiological reasons have been described for recurrent miscarriage but important to notice is that there still are unexplained cases. Genetic fetal abnormalities, most commonly fetal aneuploidy is the most important cause and as mentioned before accounts for approximately 50% of all miscarriages (52). In 19% of cases, recurrent miscarriage is shown to be due to maternal congenital or acquired uterine abnormalities (55). Maternal endocrine abnormalities, such as uncontrolled diabetes mellitus, hyperprolactinemia, and thyroid dysfunctions can also contribute to causing recurrent miscarriage. There might also be a link between polycystic ovarian syndrome and recurrent miscarriage, a study showed that women with polycystic ovaries had higher incidence of recurrent miscarriage compared to women without. Antiphospholipid antibody syndrome (APLS) is another very important cause, accounting for 8-42% of all recurrent miscarriages, APLS increases the risk for thrombosis and placental insufficiency thus leading to pregnancy loss. Environmental factors such as cigarette smoking, alcohol consumption, and obesity also increases the risk for recurrent miscarriage (52,62).

1.3.9. Intrauterine fetal demise

Fetal death, intrauterine fetal demise, and stillbirth are terms used interchangeably, they are defined as loss of pregnancy after 20th week of gestation, with a fetus weighting more than 500 grams without vital signs. We can classify them into early and late stillbirth, with the former one occurring between 20 to 27 weeks of gestation and the latter one from 28 weeks to 36 completed weeks of gestation (63). Intrauterine fetal demise affects 1 in 160 births and 98% occur in low- and middle-income countries (63,64). It is estimated that 2.6 million stillbirths occur annually worldwide. In women with a history of a previous stillbirth, the risk for stillbirth is higher compared to women without an obstetric medial history for stillbirth (64).

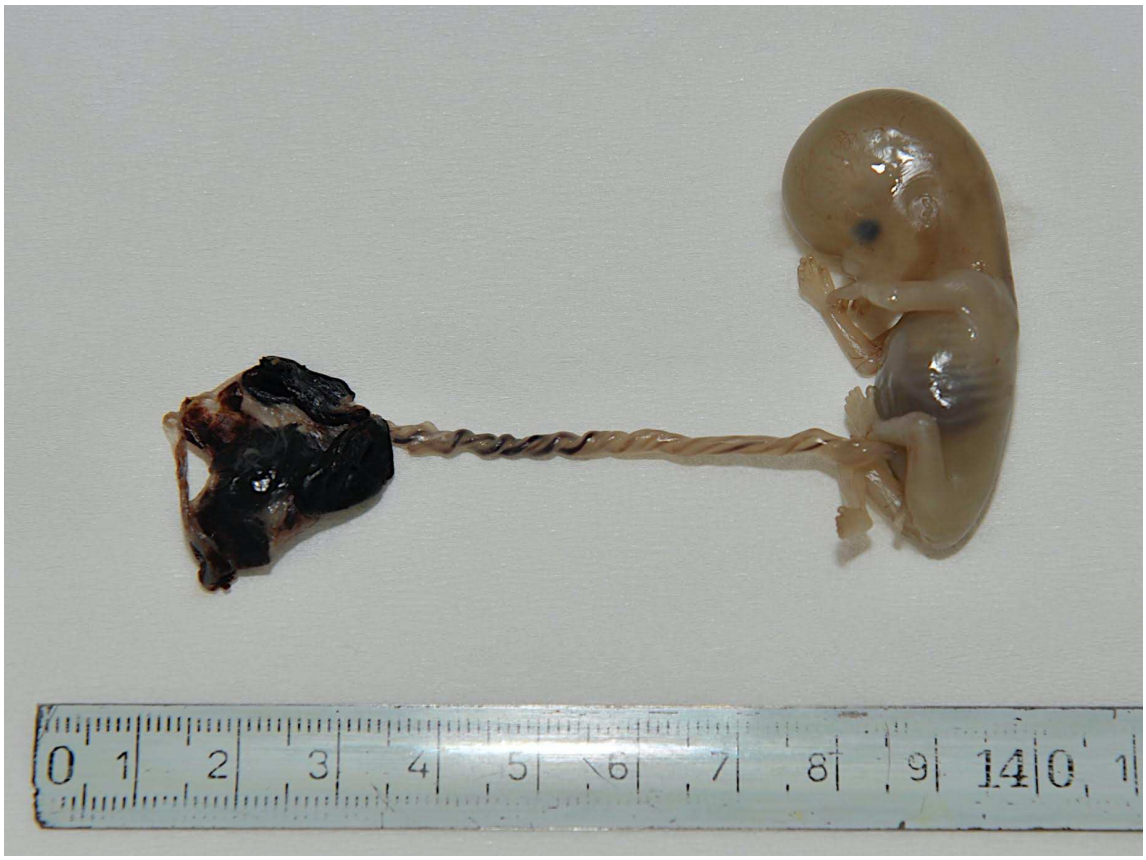

Figure 4. Intrauterine fetal demise due to hypertorsion of the umbilical cord.
(Figure is taken from mentor's archive)

1.4. Perinatal death

The term perinatal death covers late stillbirths and early neonatal death. This is the period between 28 weeks of gestation and infant age under 7 days after delivery. Rates of perinatal mortality are calculated by counting the number of deaths in the specific period per 1000 live births (65). Many classifications system have been used to simpler identify and diagnose the cause of perinatal death, however these classifications system have not been as helpful as one would think due to poor comparability. Thus, national rate of stillbirths being classified as unexplained, or unknown is two-thirds (64).

Wigglesworth, Tulip, PSANZ-PDC, Aberdeen, CODAC, and ReCoDe stillbirth classifications are all classification systems in use. These six systems were compared to each other in a study, it was concluded that Wigglesworth and Aberdeen got the lowest score due to highest proportion of categorizing stillbirth as unexplained (66). In a cohort study published in 2005 it was reported that Wigglesworth classification, a pathophysiological classification system, showed that 66% of stillbirths were classified as unexplained, consistent with the

national rate (67). On the other hand, CODAC, PSANZ-PDC, ReCoDe received higher score and had a lower rate of unexplained stillbirths. (66)

In this study, ReCoDe classification system will be used, it classifies stillbirths in Relevant (Re) Conditions (Co) at Death (De) and it is exclusively used for stillbirth classification. This system aims to identify the condition of the fetus at the time of death in utero. It does not investigate and clarify why it happened but focuses on what went wrong and what caused the stillbirth. Furthermore, ReCoDe was developed by perinatal institute in hope of improving our understanding of causes of stillbirth and by that decrease the percentage of stillbirths classified as unexplained. A study reported that ReCoDe classification system classified only 15% of stillbirths as unexplained, compared to Wigglesworth with 66% of stillbirth as unexplained (67).

As shown in Table 1, ReCoDe classification system classify the causes in alphabetical order, starting with fetus being the letter A. There are nine categories (A-I) with each of these having up to eight subcategories that describes pathophysiological cause. For example, a stillbirth with evidence of fetal growth restriction and anomalies of maternal uterus will be coded A7 E2 (67).

Fetal growth restriction was the most frequent reason for stillbirth in a cohort study conducted in 2019 when using ReCoDe classification system. Uteroplacental insufficiency was present in each of these cases. Hypertensive disease of pregnancy is the second most common cause of stillbirth (68,69). According to WHO, less than 10% of stillbirth reported nationally are caused by congenital abnormalities (70).

Table 1. Perinatal death classification according to ReCoDe classification system (67).

Group	Subgroup
A. Fetus	1. Congenital anomalies 2. Infection 3. Non-immune hydrops 4. Isoimmunization 5. Fetomaternal haemorrhage 6. Twin-twin transfusion 7. Fetal growth restriction
B. Umbilical cord	1. Prolapse 2. Constricting loop or knot† 3. Velamentous insertion 4. Other
C. Placenta	1. Abruptio 2. Praevia 3. Vasa praevia 4. Other "placental insufficiency" 5. Other
D. Amniotic fluid	1. Chorioamnionitis 2. Oligohydramnios 3. Polyhydramnios 4. Other
E. Uterus	1. Rupture 2. Uterine anomalies 3. Other
F. Mother	1. Diabetes 2. Thyroid diseases 3. Essential hypertension 4. Hypertensive diseases in pregnancy 5. Lupus or antiphospholipid syndrome 6. Cholestasis 7. Drug misuse 8. Other
G. Intrapartum	1. Asphyxia 2. Birth trauma
H. Trauma	1. External 2. Iatrogenic
I. Unclassified	1. No relevant condition identified 2. No information available

2. OBJECTIVES

2.1. Aim

This study was conducted to investigate if there was any difference in incidence of unfavorable outcomes in pregnancy such as miscarriage, intrauterine fetal demise, and early neonatal death, the year before and the year during SARS-CoV-2 pandemic at University Hospital of Split, Croatia.

2.2. Hypothesis

We hypothesized that the incidence of unfavorable pregnancy outcomes would increase during the year of SARS-CoV-2 pandemic compared to the previous year.

3. MATERIAL AND METHODS

3.1. Study design

This study is a cross-sectional retrospective study conducted at University Hospital of Split at the department of Pathology, Forensic and Cytology. All data that was collected were from the period of 1st of March 2019 to 1st of March 2021.

3.2. Materials

Our study included all pregnant women who had an unfavorable pregnancy outcome such as miscarriage and intrauterine fetal demise, as well as early neonatal death at University Hospital of Split in the time frame already mentioned.

3.3. Methods of collection of data

Collection of data for this study was extracted from the department of Pathology, Forensic and Cytology as well as department of Gynecology and Obstetrics at University Hospital of Split. Inclusion criteria where all miscarriages (complete or noncomplete), intrauterine fetal demise and early neonatal death with fetus death within 7 days of life, where tissue had been analyzed at the department of Pathology, Forensic and Cytology. Exclusion criteria are all cases where medical records were not obtained and/or those without a histopathological record, thus those without an autopsy, as well as those who underwent an induced abortion. From medical records at department of Gynecology and Obstetrics women with unfavorable outcomes in their pregnancy were extracted and we recorded the maternal age, gestational week, and information about previous miscarriage. From the archive of medical records at department of Pathology, Forensic and Cytology we extricated stillbirths and early neonatal death. From these reports we noted descriptive information regarding sex of the fetus, gestational age (in weeks), age of neonate (in hours or days, in cases where patient was born alive), as well as cause of death. After this data was obtained it was further processed into tables with the use of Microsoft Excel where additional analyses were made.

Although ReCoDe classification system is generally used to classify stillbirth, we used it to classify all the perinatal cases, including early neonatal death. We were able to allocate each case in ReCoDe category without significant data dispersion. Since classifications systems used for perinatal death have many categories and subcategories, and usually utilized for perinatal death statistics on a national level with a large study group and many cases involved,

it would have been inappropriate to use them in our study due to lower number of perinatal death cases.

3.4. Statistical analysis

Statistical analyses of the data were performed using MedCalc software (MedCalc software, Ostend, Belgium). Data distribution was estimated using Kolmogorov-Smirnov test. To interpreter the statistical significance t-test was used for normal distribution of data and Mann-Whitney U test was used for data without normal distribution. $\chi 2$-square test (also called chi-squared test) was used to estimate the qualitative variables among the different groups. Data is presented as arithmetic mean with standard deviation (SD) or as a median with minimum and maximum values. The statistical significant value was set at $P<0.05$.

3.5. Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Review Board of University Hospital of Split with reference No. 2181-147/01/06/M.S.-22-02.

4. RESULTS

This study included unfavorable outcomes of pregnancy. The time frame from 1st of March 2019 to 29th of February 2020 was referred to as the group before COVID-19 pandemic and the time frame from 1st of March 2020 to 1st of March 2021 was referred to as the group during COVID-19 pandemic. Unfavorable outcomes of pregnancies were further divided into miscarriages/abortions and loss of pregnancies that occurred after 21st gestational week and onwards, including early neonatal death.

During the investigated period there was a total of 691 miscarriages, with 392 (56.7%) occurring in year before COVID-19 pandemic and 299 (43.3%) occurring in the year during COVID-19 pandemic. The rest of the demographic data are presented in Table 2.

All patients who experienced a miscarriage or stillbirth were tested for COVID-19 infection. Out of all pregnant women with miscarriage during COVID-19, only 2 patients tested positive on SARS-CoV-2 infection at the time of the miscarriage. All patients who had a stillbirth tested negative on SARS-CoV-2 infection at the time of stillbirth.

Table 2. Demographic data for the patients who had miscarriage in the year before and during COVID-19 infection

	Before COVID-19 N=392	During COVID-19 N=299	*P*
Mother's age (years)	33 (16-46)	34 (17-46)	0.217‡
Gestational week at the time of the miscarriage	9 (5-14)	9 (5-15)	0.647*
Gravidity			<0.001†
0	82.6%	53.5%	
1	8.4%	20.1%	
2	5.1%	15%	
3	2%	8.7%	
4	1%	1.3%	
5	0.5%	0.3%	
6	0.3%	0.7%	
7	0	0	
8	0	0.3%	
Parity			<0.001†
0	85.2%	61.9%	
1	9.2%	19.4%	
2	3.6%	13.4%	
3	1%	4.3%	
4	0.5%	0.3%	
5	0.5%	0.7%	
Previous miscarriage/s			<0.001†
0	93.6%	83.6%	
1	4.8%	9.7%	
2	0.8%	5.4%	
3	0.8%	1.3%	
Habitual miscarriage	0.8%	1.3%	0.267†

‡Mann-Whitney U test;
*Student's t-test;
†Chi-square test

There was no statistically significant difference in the maternal age (z=1.235; P=0.217), gestational week at the time of miscarriage (t=0.468; P=0.647) and frequency of habitual miscarriages (χ^2=1.217; P=0.267) between the two studied groups.

Majority of the patients that had miscarriage in both groups didn't have previous gravidity in their anamnesis. However, in the year during COVID-19, there was statistically significant increase of patients who were pregnant at least one or two times prior to this miscarriage compared to the patients in the year before COVID-19 (χ^2=47.683; P<0.0001). Likewise, patients who had miscarriage during the year of COVID-19 had a higher frequency of previous parity and previous miscarriage compared to the patients who had miscarriage in the year before COVID-19 pandemic (χ^2=54.004; P<0.0001) (χ^2=21;174 P<0.0001).

Demographic data for the unwanted pregnancy outcomes after 21st gestational week are presented in Table 3.

Table 3. Demographic data for the fetal and neonatal death in regard of COVID-19 pandemic

	Before COVID-19 N=47	During COVID-19 N=49	*P*
Gestational age (week)	27±6	26±6	0.376*
Gender M:F	25:22	27:22	0.986‡
Stillbirth	21 (45%)	28 (57%)	0.309‡
Neonatal death	Early 21 Late 5	Early 19 Late 2	0.605‡

*Student's t-test;
‡Chi-square test

There was no statistically significant difference between studied groups in regard to the gestational week (t=0.859; P=0.376), gender (χ^2=0.000; P=0.986), stillbirth (χ^2=1.034; P=0.309), and early or late neonatal death (χ^2=0.268; P=0.605).

Causes of perinatal death were classified according to ReCoDe classification system. There was no statistically significant difference between studied groups as shown in Table 3 (χ^2=5.426; P=0.366). Likewise, there was no statistically significant difference between studied groups in regards of ReCoDe subclassification for every perinatal cause of death as follows: fetus category (χ^2=5.741; P=0.219), umbilical cord category (χ^2=0.006; P=0.936), placenta

category (χ^2=0.001; P=0.975), amniotic fluid category ((χ^2=1.021; P=0.312), and unclassified category (χ^2=0.703; P=0.402).

Table 4. Perinatal death classification according to ReCoDe classification and COVID-19 pandemic

Categories	Before COVID-19 N=47	During COVID-19 N=49	*P*
Fetus	15 (32%)	10 (20%)	
Congenital anomalies	4	6	
Perinatal infection	7	2	
IUGR	1	0	0.219‡
Twin-Twin syndrome	1	2	
Non-immune hydrops	2	0	
Umbilical cord	6 (13%)	7 (14%)	
Loop or Knot	0	1	0.936‡
Other	6	6	
Placenta	7 (15%)	12 (25%)	
Abruption	2	2	0.975‡
Other	5	10	
Amniotic fluid	18 (38%)	15 (31%)	0.312‡
Uterus	0	0	
Mother	0	1 (2%)	
Unclassified			
No relevant condition found	1 (2%)	4 (8%)	0.402‡
Insufficient information			

IUGR= intrauterine growth restriction
‡chi-square test

In the umbilical cord category, namely in the subgroup „other“ referred to hypertorsion of umbilical cord and causative fetal vascular malperfusion for both studied groups. Total of 15

perinatal deaths were classified as „other“ in the placenta category, all of them had maternal vascular malperfusion.

5. DISCUSSION

In the beginning of COVID-19 pandemic, medical doctors and researchers were concerned that COVID-19 would have a negative impact on pregnant women and their unborn child. It was wildly discussed worldwide, and research is still conflicting. It is already known that miscarriage is a frequent outcome in pregnancy, occurring in 10% of pregnancies that are clinically recognized and diagnosed, intrauterine fetal demise and perinatal death are also possible unfavorable outcomes (22).

At University Hospital of Split, all pregnant women who underwent a medical abortion during the year of COVID-19 were tested for SARS-CoV-2 prior to the admission. However, only 2 patients tested positive at the time of miscarriage. The results in this study showed that out of the 691 miscarriage that occurred during the time investigated, 392 (56.7%) of these occurred the year before COVID-19 and 299 (43.3%) the year during the pandemic. The somewhat lower number of miscarriages during the year of COVID-19 pandemic may reflect the fact that visits to the gynecologist also reduced during this time. This could have been because being around and inside hospital settings was associated with increased risk for getting infected with COVID-19, a risk some pregnant women didn't want to take. Thus, there is a possibility that some women had an early miscarriage without even noticing it themselves, resulting in them not seeking medical care, thus leading to no medical report of their miscarriage. Likewise, they could have mistaken their early miscarriage with menstruation and thereby did not report it to their general practitioner or gynecologist. Also, during COVID-19 pandemic the hospital was limited, and resources were cut short, so, if possible, cases with uncomplicated miscarriage were handled by primary care gynecologist (34,35,52,53).

Our study showed that in both groups that were investigated, majority of patients who had miscarriage had no prior gravidity in their obstetrical anamnesis. During the year of COVID-19 pandemic there was a statistically significant increase of patient who had been pregnant at least once or two times prior to this miscarriage. These findings can be explained by the fact that patients who have experienced a previous pregnancy are more aware of the different symptoms and signs associated with early pregnancy and are thus more prone to seek medical attention. This in turn leads to miscarriage being reported in the medical archive and does not go undocumented. Aforementioned could also explain the fact that a higher frequency of previous parity and previous miscarriage was seen during the pandemic compared to the year before.

There was no statically significant difference in gestational week at the time of miscarriage when comparing the group before COVID-19 pandemic with the group during COVID-19 pandemic. Also, there was no statistical significance difference in maternal age or

frequency of in the frequency of habitual miscarriage. These results were expected since data like this is actually a constant that does not usually change frequently, especially not in a small sample size and during a short and limited period of time.

A systemic review reported an increase rate of stillbirth in pregnant patients during the pandemic compared to before the pandemic, and it was concluded that this was due to a delay in healthcare because of COVID-19 pandemic. The above-mentioned study conflicts with a study conducted in the United States, which claimed that the rate of stillbirth before COVID-19 pandemic closely resembled the incidence during the pandemic. Our study is in accordance with the latter mentioned study as no statistically significant difference was seen in the studied groups regarding incidence of stillbirth. Also, no significant difference in incidence of early and late neonatal death was seen. This shows that despite the COVID-19 pandemic and its stressful and negative effect in association with the increase workload did not affect pregnant women seeking medical care at University Hospital of Split. Pregnant patients still got provided with adequate healthcare throughout their pregnancy and were not affected by the pandemic in the means of an increase incidence of stillbirths or early neonatal death. Additionally, since stillbirth is defined as loss of pregnancy after gestational week 20, at this time most of pregnant women are aware that they are pregnant and would thereby most probably go to regular checkups. This could in turn decreases the likelihood for a stillbirth (38,39).

Furthermore, we noted that out of all stillbirths occurring during the year of the pandemic, none of the pregnant women tested positive for COVID-19 infection at the time of the occurrence. However, it should be noted that there were SARS-CoV-2 infected pregnant patient at the department of gynecology and obstetrics at the hospital as well as outside of the hospital, included in this study, but none of those pregnancies ended in a stillbirth. This further emphasizes the qualitative care provided by University Hospital of Split to pregnant patients during the pandemic (38).

Cause of perinatal death, classified with ReCoDe classification system, showed no statistically significant difference between the studied groups. However, according to national data, fetal category, more specifically the subcategory “intrauterine growth restriction” is the major cause of perinatal death. Our study contradicts this showing that category of “amniotic fluid” and its subcategory “chorioamnionitis” accounts for majority of perinatal deaths with 18 (38%) and 15 (31%) the year before and the year during COVID-19 pandemic, respectively. Moreover, national data describes that when ReCoDe classification system is utilized, only 15% of all stillbirths are classified as unknown, our study shows an even superior result with 2%

being classified as unknown the year before COVID-19 pandemic and 8% during the pandemic (66,68,69).

The present study contains some limitations. The main limitation is the retrospective-design used, which is dependent on accurate data keeping in medical database or medical archive, and not collected to be used for research purpose. Thus, this data was not collected in a predesigned form as per the specific requirements for a research study and is prone to bias due to mistakes, missing data, and imprecision. For instance, some medical records lacked the SARS-CoV-2 test result, and for a more detailed insight all that documentation should have been saved and gather. Furthermore, our study included only one facility i.e. University Hospital of Split with a small sample size. Ideally, more facilities should have been included in this study. Another limiting factor is that not all samples are sent to the department of Pathology, Forensic and cytology making it difficult to gather information. Therefore, it is of the utmost importance to have an outstanding cooperation between departments at the hospital, and that all tissues, samples, placentas, and fetus are sent to department of Pathology, Forensic and cytology for further autopsy and ideally identification of cause of death.

6. CONCLUSION

No statistically significant difference in the incidence of unfavorable outcomes in pregnancy the year before and the year during COVID-19 pandemic at University Hospital of Split was seen in this study. Our study showed that the pandemic did not have a negative effect on pregnant women and their fetus, there was no increase in miscarriage, intrauterine fetal demise, or perinatal death the year during the pandemic. This does not confirm our hypothesis but nevertheless shows that University Hospital of Split gave pregnant women the same quality healthcare that they need, all this despite an ongoing pandemic.

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8. SUMMARY

Objectives: To investigate if the incidence of unfavorable pregnancy outcomes and perinatal death differed the year before the start of COVID-19 pandemic compared to the year during COVID-19 pandemic.

Materials and Methods: This was a cross-sectional retrospective study conducted at department of Pathology, Forensic and Cytology at University Hospital of Split within the time span of March 1st 2019 to March 1st 2021. Data was collected from department of Pathology, Forensic and Cytology and department of Gynecology and Obstetrics. All miscarriages, intrauterine fetal demise and early neonatal death were obtained together with more specific information such as: gestational week of fetus or age of neonate, mothers age, gender, as well as previous obstetrical anamnestic data. Exclusion criteria where cases that lacked medical and histopathological records, and induced abortions. ReCoDe classification system was used to classify cases of perinatal death.

Results: This study included unfavorable pregnancies outcomes; miscarriage and intrauterine fetal demise, as well as early perinatal death. Study groups were divided in two groups, the first group referred as before COVID-19 pandemic and spanned from 1st of March 2019 to 29th of February 2020, and the other group referred as during COVID-19 pandemic and covers time frame from 1st of March 2020 to 1st of March 2021. During the investigated period, 691 miscarriages occurred, 56.7% before and 43.4% during COVID-19 pandemic. In miscarriage there was no statistical difference in maternal age, gestational weeks, and incidence of habitual miscarriages between the two groups. However, in the year during COVID-19 statistically significant increase of patients who were pregnant at least one or two times prior compared to year before. ($P<0.0001$). They also had a higher frequency of previous parity and miscarriage. No statistically significant difference between the two groups studied in regard to stillbirth and early/late neonatal death Likewise, there was no statistically significant difference between studied groups in regards of ReCoDe subclassification for every perinatal cause of death.

Conclusion: There was no increase in unfavorable outcomes during pregnancy when comparing the group before and the group during COVID-19 pandemic which points that the healthcare for pregnant women treated at University Hospital of Split during COVID-19 did not differ compared to the year before.

9. CROATIAN SUMMARY

Naslov: Nepovoljni ishodi trudnoča u KBC Split u razdoblju od 2019. godine do 2020. godine obzirom na COVID-19 pandemiju.

Ciljevi: Istražiti postoji li razlika u učestalosti nepovoljnih ishoda trudnoće i perinatalne smrti godinu dana prije početka pandemije COVID-19 u odnosu na godinu tijekom pandemije COVID-19.

Materijal i metode: Retrospektivna studija, provedena je na odjelu Patologije, Kliničkog zavoda za patologiju, sudsku medicinu i citologiju, KBC Split, u razdoblju od 1. ožujka 2019. godine do 1. ožujka 2021. godine. Podaci su prikupljeni na odjelu patologije, te klinike za ženske bolesti I porode. U studiji su uključeni svi spontani pobačaji, mrtvorođeni i rana neonatalna smrt, te zabilježena je gestacijska dob, dob i spol novorođenčeta, spol, dob majke, i prethodni opstetrički anamnestički podaci. Kriteriji isključenja su bili svi slučajevi bez dostatne medicinske dokumentacije i/ili ukoliko analiza materijala nije učinjena na odjelu za patologiju.

Rezultati: Studija je uključila nepovoljne ishode trudnoće; spontani pobačaj i intrauterina smrt fetusa, i rana perinatalna smrt. Ispitivane skupine su podjljene na sljedeći način: prva skupina se odnosila na razdoblju prije pandemije COVID-19, od 1. ožujka 2019. do 29. veljače 2020., a druga skupina se odnosila na razdoblje pandemije COVID-19 i pokriva vremenski okvir od 1. ožujka 2020. do 1. ožujka 2021. Tijekom istraživanog razdoblja zabilježeno je 691 pobačaja, 56,7% prije i 43,4% tijekom pandemije COVID-19. Nije bilo statistički značajne razlike u dobi majke, gestacijskoj dobi ili učestalosti pobačaja između isitivanih skupina. U skupini tijekom COVID-19 pandemije bilo je više pacijentica koje su imale prethodne trudnoće u odnosu na godinu prije, što je bilo statistički značajno ($P<0,0001$).
Također su imale veću učestalost prethodnog pariteta i pobačaja. Nije bilo statistički značajne razlike obzirom na perinatalnu smrtnost, kao ni klasifikaciju iste prema ReCoDe klasifikaciji između ispitivanih skupina.

Zaključci: Nije zabilježen porast nepovoljnih ishoda trudnoće u godini za vrijeme COVID-19 pandemije u usporedbi skupine, što ukazuje da se zdravstvena zaštita trudnica liječenih u KBC ostala na zavidnoj razini unatoč teškim uvjetima zbog COVID-19 pandemije.

10. CURRICULUM VITAE

General information:

Name and surname:	Emma Mulic
Date of birth:	1st of August 1996
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Address:	Tyrsjövögen 22B, 42472 Göteborg, Sweden
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Education:

2015 – 2022	University of Split, School of medicine
2015 – 2016	Högskolan I Halmstad, Biomedicin med inrikning fysisk träning
2012 – 2015	Polhemsgymnasiet, Naturvetenskap, Göteborg

Work experience:

01-03/2022	Erasmus student at Norra Älvsborgs Länssjukhus
06-09/2020	Medical assistant at Capio Läkarhus Selma Vårdcentral
09/2019	Medical assistant at Capio Läkarhus Selma Vårdcentral
03-08/2016	Inspection and Damage Control

Personal skills and competence:

Mother tongue:	Swedish
Other language:	Croatian, English
Driver license:	Category A, B
2017 – 2021	Class representative and member of student council
2019 – 2021	Member of faculty council