HEALTH, ENVIRONMENT, DEVELOPMENT

CONGENITAL AND HEREDITARY PATHOLOGY IN WOMEN CONTRACTED COVID-19 DURING PREGNANCY

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Summary

he study aimed to investigate the frequency and structure of congenital and hereditary pathologies identified through non-invasive and invasive methods of prenatal diagnostics in women who contracted COVID-19 during pregnancy, among the population of the Lviv region. The data from prenatal diagnostics results of congenital developmental defects in non-invasive prenatal diagnostics and hereditary diseases in invasive prenatal diagnostics were analyzed in women who contracted COVID-19 during pregnancy. The study demonstrated that the frequency of diagnosing congenital anomalies (CA) in the fetus among 159 pregnant women in non-invasive prenatal diagnostics (PND) was 13.8%.

In the structure of congenital anomalies, facial anomalies were the most prevalent, accounting for 5.0% in the first position, followed by anomalies of the cardiovascular system at 2.5% in the second position, anomalies of the skeletal system at 2.5% in the third position, and multiple congenital anomalies at 1.9% in the fourth position. Invasive prenatal diagnostics were performed on 12.6% of women in this group, with chromosomal pathology detected in 5.0% of women: trisomy 21 was diagnosed in 3.8%, Turner syndrome in 1.3%, and a normal karyotype was identified in 7.5% of patients. The frequency of chromosomal pathology in women who contracted COVID-19 during pregnancy was 5.0%. The results of this study will contribute to the improvement of effective medical-genetic counseling and the prediction of healthy offspring.

Key words: pregnancy, congenital anomaly, hereditary diseases, prenatal diagnostics, COVID-19

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1. Introduction

The demographic crisis observed in Ukraine is significantly exacerbated by reproductive losses, resulting in an increased frequency of offspring with congenital and hereditary pathology. This leads to early disability (*Zaporozhan V.M. et al., 2012; Tymonina M.B., 2016; Pidvysotska N.I.,2015*). In Ukraine, perinatal and child mortality rates exceed those in European countries *(Lazoryshynets V.V., 2016)*. Among the causes of early neonatal child mortality, congenital anomalies (CA) incompatible with life dominate *(Verteletskyi V., et al., 2016).* The need for effective prenatal diagnostics and the study of factors contributing to congenital anomalies are determined by the scale of their prevalence and their impact on children's survival in the postnatal period.

The World Health Organization (WHO) has developed a Risk Approach Strategy aimed at identifying the causes of various complications during pregnancy and labor, as well as finding ways to improve the effectiveness of maternal and child health care. In these circumstances, reducing perinatal mortality, and preserving the lives and health of newborns is a necessary condition for the demographic development of Ukraine and a factor in national security *(Medvedev, M.V. et al., 2016; Safonova I.N., 2016).*

In 2019, the World Health Organization (WHO) confirmed the name COVID-19 (short for Coronavirus Disease 2019) for the illness caused by the SARS-CoV-2 infection *(Sonja A. Rasmussen et al., 2020)*. Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome due to the infection with the SARS-CoV-2 coronavirus, rapidly spread worldwide, and on March 12, 2020, the WHO declared the outbreak a pandemic (*Dehan Liu et al.,2020*). Since pregnant women are at a higher risk of experiencing a complicated course of coronavirus infection, they have been identified as a high-risk group *(Sudheer R. Gorla et al., 2019; Heather Y. et al., 2018; Wong S.F. et al., 2004)*.

As of today, there is limited and conflicting data regarding the potential for physiological adaptation of pregnancy to the conditions of infection, the severity of acute respiratory syndrome, and the likelihood of complications in pregnant women with COVID-19. Pregnant women are considered potentially vulnerable to a severe course of acute respiratory infection with SARS-CoV-2 due to physiological changes during pregnancy that significantly affect the activity of the immune system, respiratory, cardiovascular, and excretory functions, as well as blood coagulation (*Huang C. et al.,2020; Lei D.W.C. et al.,2020*).

Asymptomatic infection poses another challenge for service provision, prevention, and management. In addition to the direct impact of the disease, numerous indirect consequences of the pandemic negatively affect maternal health, including reduced access to reproductive health services, increased mental health strain, and heightened socio-economic deprivation *(Sonja A. Rasmussen et al., 2020)*. It is suggested that these changes may have both negative and positive effects on the course of COVID-19, but this is not conclusively supported by evidence-based medicine. The impact of acute respiratory disease SARS-CoV-2 on pregnancy still requires extensive study and confirmation in various aspects, including its influence on implantation, fetal growth and development, as well as the health status of newborns *(Dehan Liu et al., 2020)*. Severe perinatal complications (premature births, stillbirths) in COVID-19 are attributed to gestosis with characteristic disruptions in the course of pregnancy, such as preeclampsia, hypertension, and proteinuria *(Wastnedge E.A.N. et al., 2021)*. In women with gestosis, insufficient reduction in vascular resistance is observed in the middle and late stages of gestation, associated with endothelial dysfunction *(Guo Z-D., et al., 2020).*

Pregnancy is a state of hypercoagulability characterized by increased thrombin generation and enhanced intravascular inflammation. During pregnancy, there are higher levels of circulating coagulation and fibrinolytic factors, which may be implicated in the pathogenesis of SARS-CoV-2 infection *(Bourne T. et al., 2020)*. Pregnant women have an elevated risk of thromboembolic events, which could be associated with mortality *(Poon L.C. et al., 2020)*. Therefore, pregnant women with COVID-19 may experience a synergy of thrombosis risk factors. Current recommendations suggest that all pregnant women with confirmed COVID-19 should receive thromboprophylaxis for up to 10 days postpartum, with a low threshold for investigating potential thromboembolism *(Poon L.C. et al., 2020)*.

Despite the lack of data on placental changes in COVID-19 infection, researchers have described placental pathology in SARS in Hong Kong *(Cascella M. et al., 2020)*. The conducted study is the first to examine pathological changes in the placenta in SARS-CoV-2 infection. The authors describe an elevated level of fibrin deposits around chorionic villi, large areas of avascular villi, and sometimes identified significant infarction in the villi, along with an increased level of erythrocytes in the fetal umbilical cord *(Cascella M. et al., 2020; Di Mascio D. et al., 2020)*.

In studies by various researchers, the leading role of prenatal ultrasound examination of pregnant women in diagnosing prenatal pathology and congenital anomalies (CA) has been demonstrated *(Cascella M. et al., 2020; Di Mascio D. et al., 2020; Safonova I.M., 2015)*. Ultrasound examination (UE) remains the most widely used form of mass screening for pregnant women today *(Safonova I.M., 2015; Hrabar V.V., 2015; Nikolenko M.I. et al., 2018)*. However, the increase in the number of UE has not significantly affected the quality of prenatal diagnosis of congenital anomalies due to the relatively low overall number of prenatally detected cases *(Begimbekova L.M. et al., 2015; Pasiieshvili, N.M., 2016)*.

Scientists have conducted several studies examining the effectiveness of prenatal diagnosis of critical congenital anomalies (CA) and errors in ultrasound examinations (UE) *(Pasiieshvili, N.M., 2016)*. Key factors influencing the accuracy of prenatal CA diagnostics include the qualifications of the specialist and the quality of visualization. A two-tier system of prenatal diagnostics allows for a highly accurate determination of congenital heart defects. However, the system functions with limited efficiency.

Researchers emphasize in their works that early diagnostics of congenital anomalies is a significant reserve for reducing childhood morbidity, disability, and mortality *(Lazoryshynets V.V., 2016; Nikolenko M.I., et al., 2018; Prokopchuk N. et al., 2023)*.

Qualified non-invasive and invasive prenatal diagnostics with established diagnoses of anomalies allow for timely organization of professional assistance for children with CAs, deliveries in specialized centers equipped for such therapy or surgical intervention, and contribute to improving perinatal morbidity and mortality rates (*Lazoryshynets V.V., 2016;Kovalenko O.S. et al., 2016*).

The prognosis for congenital anomalies is relatively favorable when detected early, and the possibilities for radical treatment are promising. In the absence of such possibilities, the outlook is dubious or unfavorable *(Kovalenko O.S. et al., 2016)*. Therefore, the necessity for early prenatal detection of CAs is crucial. It allows for decisions on the advisability of maintaining the pregnancy and, in case of its continuation, devising the most appropriate tactics for its further management.

Since 1979, monitoring of the frequency of births with congenital anomalies has been conducted in 22 European countries. All these conditions are registered in the unified European

register – EUROCAT (European Surveillance of Congenital Anomalies). To objectify the research, EUROCAT takes into account developmental defects in the fetus that can affect the formation of prenatal and infant mortality and may also be a cause of human disability. These defects are referred to as 'model' anomalies *(Loane M., 2011)*.

Only a few regions in Ukraine provide their data on the frequency of congenital anomalies to EUROCAT. Therefore, studying the epidemiology of congenital anomalies, including chromosomal disorders; researching the impact of various nosological forms of congenital pathology on perinatal and child mortality; identifying new teratogenic risk factors for CAs; and developing modern screening programs for prenatal diagnosis and pregravid prognosis for women are relevant tasks in modern medicine.

Although most developmental abnormalities are related to pathology that is relatively well diagnosed by non-invasive methods of prenatal diagnosis (ultrasound screening), unfortunately, a late manifestation of pathology often occurs. This does not allow for timely prevention of the birth of a sick child with pathology, leading to persistent disability *(Nikolenko M.I., et al., 2018)*.

It is essential not only to obtain and accumulate data on the study of congenital anomalies but also to improve modern methods of prevention and early diagnosis of congenital pathology in families at risk *(Antipkin Y.G. et al., 2018).*

Prenatal diagnosis of congenital and hereditary pathology, a comprehensive examination of the fetus with the most accurate prognosis for life and health, is a necessary element of quality care during pregnancy and childbirth.

Application of modern methods of prenatal diagnostics in the comprehensive diagnosis of complex CAs in the fetus, taking into account the prospects of postnatal correction for children with congenital malformations in women who contracted COVID-19 during pregnancy, will be a reserve for reducing morbidity and disability in children *(Kostiuk O.O. et al., 2020)*.

It is considered expedient to conduct a study on the frequency and structure of congenital and hereditary pathology diagnosed by non-invasive and invasive methods of prenatal diagnosis in women who contracted COVID-19 during pregnancy. This study aims to determine the impact of this condition on the structure of perinatal pathology in the population of the Lviv region, Ukraine.

The aim of the research. Investigation of the frequency and structure of congenital and hereditary pathology detected by non-invasive and invasive methods of prenatal diagnosis in women who contracted COVID-19 during pregnancy.

To achieve this, the following *tasks* were set:

1. Creation of a registry of women who contracted COVID-19 during pregnancy from Lviv city and the districts of Lviv region based on ultrasound screening data.

2. Analysis of the frequency and structure of congenital and hereditary pathology in women who contracted COVID-19 during pregnancy, based on the results of non-invasive and invasive methods of prenatal diagnostics.

2. Results

During the period of 2022-2023, ultrasound diagnostics (UE) was conducted for a total of 159 pregnant women who contracted COVID-19 during pregnancy: UE was performed for 97 (61.0%) pregnant women up to 22 weeks of gestation and for 62 (39.0%) after 22 weeks of gestation.

Ultrasound examination of pregnant women was conducted using the Voluson E8 device, operating in real-time, with the use of abdominal, linear, and sector probes (frequency 3.5 MHz). The exposure time for ultrasound examination was 15-30 minutes. During the examination, prenatal somatogenetic fetal assessment was used according to the approach to prenatal fetal assessment. The biometric, morphological, and pathophysiological features of the fetus were thoroughly evaluated. A standard fetal assessment was performed, obtaining basic biometric indicators and describing changes in the internal organs. The amount of amniotic fluid was assessed by measuring the height of its column. Placentography aimed to determine the localization, size, and echographic structure of the placenta, as well as pathological changes within it. In the case of detecting congenital anomalies in the fetus during ultrasound examination, prenatal syndromological analysis was conducted. This entails identifying, among all the pathological signs, a cluster of clinical symptoms that enables the diagnosis of a particular syndrome involving multiple congenital anomalies (MCA).

3. Clinical characteristics of examined women

The majority of pregnant women who contracted COVID-19 during pregnancy were in the age range of 26–30 years, comprising 63 (39.6%). The distribution across age groups was nearly equal for women aged 31-35 and 36 years and older, with 38 (23.9%) and 41 (25.8%), respectively. The smallest proportion consisted of women aged 21-25 years, with 17 (10.7%). There were no women under 20 years old among those who contracted COVID-19 during pregnancy (Table 1). Regarding the place of residence, out of 159 women, an almost equal number lived in rural areas – 75 (47.2%), and in urban areas – 84 (52.8%).

Table 1

Characteristics of women who contracted COVID-19 during pregnancy, by age, place of residence, and pregnancy parity

Number of women (q-ty/%)	Age (years)				Place of residence		Pregnancy parity		
	21–25	26–30	31–35	36 or >	rural	urban	I	II	III or >
159 (100%)	17 (10.7%)	63 (39.6%)	38 (23.9%)	41 (25.8%)	75 (47.2%)	84 (52.8%)	61 (38.4%)	62 (39%)	36 (22.4%)

The study of pregnancy parity showed that the number of women with first or second pregnancies was almost equal: 61 (38.4%) and 62 (39%), respectively. In 36 cases (22.4%), the pregnancy was the third or more.

Among women who contracted COVID-19 during pregnancy, a significant number were in the age group of 26-30 years – 63 (39.6%). There were 61 (38.4%) primigravidae, 62 (39%) were in their second pregnancy, and 36 (22.4%) had three or more pregnancies.

4. Frequency and structure of congenital pathology diagnosed by non-invasive methods of prenatal diagnosis

The structure of pathology diagnosed by ultrasound in pregnant women who contracted COVID-19 during pregnancy is shown in Table 2.

Table 2

Structure of pathology diagnosed by non-invasive methods

Indicators	Number of women (q-ty/%)
Total women in the risk group	159 (100%)
No peculiarities found	32 (20.1%)
Total peculiarities found	127 (79.9%)
Premature placenta aging	28 (17.6%)
Disturbance of uteroplacental blood flow	18 (11.3%)
Combination of placental and blood flow pathology	59 (37.1%)
Congenital anomalies detected	22 (13.8%)
Multiple congenital anomalies	3 (1.9%)
CAs of the cardiovascular system	7 (4.4%)
CAs of the skeletal system	4 (2.5%)
Facial CAs	8 (5.0%)

Analysis of the data in Table 2 showed that in 127 (79.9%) women who contracted COVID-19 during pregnancy, certain peculiarities and pathological changes were identified on ultrasound, especially in the structure of the placenta and changes in uteroplacental blood flow. In 32 (20.1%) women, no peculiarities (deviations from the norm) were detected on ultrasound.

Thus, in 28 (17.6%) women, premature aging of the placenta was diagnosed on ultrasound. In 18 (11.3%), there were disturbances in uteroplacental blood flow, and in 59 (37.1%), a combination of pathologies was observed (Table 2).

Prenatal fetal anomalies were diagnosed in 22 (13.8%) women in this group. In the structure of CAs diagnosed on ultrasound in pregnant women, 7 (4.4%) had cardiovascular system anomalies, 4 (2.5%) had skeletal system anomalies, 3 (1.9%) had multiple anomalies, and 8 (5.0%) had facial anomalies.

It was found that the frequency of congenital anomalies detected through non-invasive prenatal diagnostics in women who contracted COVID-19 during pregnancy was 13.8%. The structure of CAs ranks facial anomalies first (8 – 5.0%), followed by anomalies in the cardiovascular system (4 – 2.5%), skeletal system anomalies (4 – 2.5%), and multiple anomalies (3 – 1.9%).

5. Frequency and structure of chromosomal pathology diagnosed by invasive methods of prenatal diagnostics

A total of 20 (12.6%) women out of 159 patients who contracted COVID-19 during pregnancy underwent invasive procedures.

Indications for invasive methods of prenatal diagnostics were ultrasound markers of chromosomal pathology: increased nuchal translucency (NT) in 11 (6.9%) women; hypoplastic nasal bone (HNB) in 6 (3.8%) women; in three women (3.7%), there was a combination of ultrasound markers – increased NT + HNB. For these women, amniocentesis was performed in 8 (5.0%) cases, and chorionic biopsy (CB) in 12 (7.5%) cases.

In determining the indicators of invasive prenatal diagnostics, the following results were obtained: a pathological karyotype was detected in 8 (5.0%) women in this group. Trisomy 21 was diagnosed in 6 (3.8%) women; Turner syndrome was detected in 2 (1.3%) women, and

a normal karyotype was identified in 12 (7.5%) patients (Figure 1). NIPT was performed on two (3.3%) women, and a normal karyotype was identified (Figure 1).

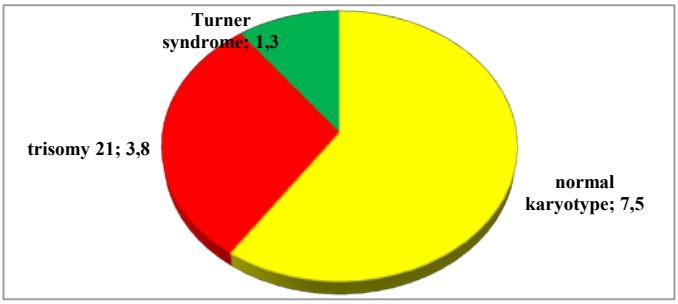

Fig. 1. Results of the fetal karyotype (invasive prenatal diagnostics)

Thus, the frequency of chromosomal pathology in women who contracted COVID-19 during pregnancy was 5.0%.

6. Conclusions

Ultrasound diagnostics were performed on 159 women who contracted COVID-19 during pregnancy. The frequency of congenital anomalies identified during non-invasive prenatal diagnostics in this group of women was 13.8%. The structure of CAs ranks facial anomalies first (8 – 5.0%), followed by anomalies in the cardiovascular system (4 – 2.5%), skeletal system anomalies (4 – 2.5%), and multiple anomalies (3 – 1.9%).

2. In 32 (20.1%) women who contracted COVID-19 during pregnancy, ultrasound examinations revealed certain features and pathological changes, most frequently in the structure of the placenta and alterations in uteroplacental blood flow. Specifically, premature aging of the placenta was diagnosed in 28 (17.6%) women, disruption of uteroplacental blood flow in 18 (11.3%), and a combination of pathologies in 59 (37.1%).

3. In 20 (12.6%) of the 159 patients who contracted COVID-19 during pregnancy, invasive interventions were performed. The indications for invasive prenatal diagnostic methods were ultrasound markers of chromosomal pathology: increased nuchal translucency (NT) in 11 (6.9%) women, hypoplastic nasal bone (HNB) in 6 (3.8%) women, and a combination of ultrasound markers (increased NT + HNB) in three (3.7%) women. Among these women, amniocentesis was performed in 8 (5.0%) cases, and chorionic biopsy (CB) in 12 (7.5%) cases.

4. The frequency of chromosomal pathology in women who contracted COVID-19 during pregnancy was 5.0%. A pathological karyotype was detected in 8 (5.0%) women of this group. Specifically, trisomy 21 was diagnosed in 6 (3.8%) women, Turner syndrome was identified in 2 (1.3%) women, and a normal fetal karyotype was identified in 12 (7.5%) patients.

Prospects for further research

The obtained data indicate the need for further refinement and improvement of the early diagnosis system for congenital anomalies, which would contribute to effective medical-genetic counseling and forecasting of healthy offspring. Individual prenatal diagnostics and monitoring the frequency of congenital anomalies can help reduce the incidence of congenital abnormalities.

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