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Review paper

Prenatal ultrasound evaluation in the current era of COVID-19 – looking only for major congenital defects or subtle sonographic and echocardiographic findings, as well?

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Abstract

Introduction: In December 2019 a novel coronavirus emerged. COVID-19 disease varies in severity. Pregnancy implicates special susceptibility to pathogens and severe pneumonia. It is rational to compare accessible literature and discuss possible prenatal ultrasound monitoring in cases of COVID-19 among gravidas.
Material and methods: A PubMed search was conducted, utilising the terms 'covid 19' and 'pregnancy'. Only original source materials were used for comparison. Collected data included: author, date of study, region of study, number of cases, gravidas' age, trimester of pregnancy during examination, chronic, concomitant diseases, symptoms of infection, type of delivery, Apgar score range, fetal problems, perinatal outcome, and the possibility of vertical transmission.
Results: From a total of 39 results initially identified, six matched our search criteria. Mothers' ages ranged from 22 to 40 years. Mostly they were healthy women, previously with COVID-19 infection, and without chronic diseases. Symptoms of COVID-19 were similar to those presented in the general population: fever, cough, sneezing, nasal congestion, sore throat, myalgia, malaise, dyspnoea, and diarrhoea. Caesarean section constituted 93% of all deliveries. Twenty of 48 (41%) fetuses were delivered preterm. Apgar scores ranged from 7 to 10 points; only one neonate received 7 points. There is no evidence of SARS-CoV-2 vertical transmission until now.
Conclusions: Current literature does not allow for more precise description of fetal functional changes in the course of maternal COVID-19. More extensive studies are needed with special consideration of fetal cardiovascular system examination and further postnatal monitoring and more extensive epidemiological evaluation.

Key words: fetal echocardiography, fetal ultrasound, COVID-19.

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Introduction

In December 2019 a novel coronavirus, called SARS-CoV-2 emerged in China. From 10-24 January 2020, the number of people diagnosed with SARS-CoV-2 infection in China increased by 31.4 times [1]. The COVID-19 disease has widely occurred across the globe, causing significant public health and economic problems. At the time of preparing this article, COVID-19 has slowed down in China, but is aggressively spreading in Europe and North America. The pandemic is still

present. Currently there have been 846,251 confirmed cases and 41,482 people have died because of COVID-19 [2].

In Poland, we have had 2311 cases and 33 people have died [2]. The Polish government has restricted social life, for example by forbidding travelling of more than two people together, except families [3]. Mostly older men are infected (Li et al. average 59 years old, 56% men) [4], so a prevalently adult affected population is described in literature, also because of more aggressive course of the disease. But now that there are more than 800,000 cases, pregnant women are being discussed, because of not only the theoretical but also the real possibility of infection. Pregnancy implicates an immunosuppressive state and physiological changes (diaphragm elevation, increased oxygen consumption, and oedema of respiratory tract mucosa), which cause susceptibility to pathogens and severe pneumonia.

The 1918 influenza pandemic caused a mortality rate of 2.6% in the overall population but 37% among pregnant women. In the more recent H1N1 influenza virus pandemic in 2009 pregnant women were four times more likely to be admitted to hospital than the general population. Moreover, around 33% of pregnant women with SARS (caused by SARS-CoV) required mechanical ventilation, and the mortality rate was as high as 25% for these women [5].

For now, no publication concerning infected pregnant women in Poland is available on PubMed, probably because of the less critical situation compared to other countries. The authors of this article are concerned that this is only a matter of time, unfortunately. Due to the above, it is rational to compare accessible literature and discuss possible prenatal ultrasound monitoring in cases of COVID-19 among gravidas.

The aim of this study was to evaluate the influence of COVID-19 on the course of pregnancy. On the basis of such analysis, we tried to answer whether during the COVID-19 pandemic it is possible to provide detailed fetal ultrasound and echocardiographic examination to high-risk pregnant women.

Material and methods

A PubMed search was conducted from recent publications. In order to identify all potentially relevant articles regarding the influence of COVID-19 on the course of pregnancy, the search was performed utilising the terms 'covid 19' and 'pregnancy'. Potentially relevant articles were evaluated. Only full-size articles of English language published in journals or during press processes were considered. Only original source materials were used for comparison of COVID-19 infected pregnant women.

Studies reporting single case reports were not considered. Also, cases not diagnosed by laboratory tests for SARS-CoV-2 were excluded. Collected data included: author, date of study, region of study, number of cases, gravidas' age, trimester of pregnancy during examination, chronic, concomitant diseases, symptoms of infection, type of delivery, Apgar score range, fetal problems, perinatal outcome, and the possibility of vertical transmission. Other results were used for discussion.

Results

From a total of 39 results initially identified, six matched our search criteria for original source material with more than one case report described and English language publication. Three studies were available in Chinese language, two studies presented single case reports, and two studies did not confirm all of the cases by laboratory tests for SARS-CoV-2. The individual original source study characteristics are given in Table 1 [5–10]. The studies originate from the China region between December 2019 and February 2020. In total the study included 55 pregnant women – 56 fetuses (two twins). Only one study described infected gravidas before the third trimester, but perinatal outcome was available only for third trimester fetuses.

The mothers' minimal age was 22 years and maximal age was 40 years. Mostly they were: previous to COVID-19 infection, healthy women, and without any chronic disease (one gestational hypertension, one gestational diabetes, one preeclampsia, one thalassemia with gestational diabetes, one after tricuspid and mitral valvular replacement, one complete placenta previa, one hypothyroidism, one polycystic ovary syndrome, one H1N1 coinfection, one *Legionella pneumophila* coinfection, and three uterine scars). Symptoms of COVID-19 were similar to those presented by the general population: fever, cough, sneezing, nasal congestion, sore throat, myalgia, malaise, dyspnoea, and diarrhoea. Caesarean section constituted 93% of all deliveries. Twenty of 48 (41%) fetuses were delivered preterm. Apgar scores ranged from 7 to 10 points; only one neonate received 7 points.

Discussion

Since December 2019, unexplained cases of pneumonia were reported in Wuhan, China. The pathogen was discovered to be new and was named by the World Health Organisation (WHO) as coronavirus 2019-nCoV. Later, the coronavirus study group of the International Committee on Taxonomy of Viruses named 2019-nCoV as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. At present the pandemic is spreading, with higher and higher mortality in Europe; however, original source materials are available only from China, to date.

According to the WHO, a suspect case is:

- A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath), and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; or
- A patient with any acute respiratory illness and having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; or
- A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath; and requiring hospitalisation) AND the absence of an alternative diagnosis that fully explains the clinical presentation [11].

Table 1. The individual original source study characteristics

Author	Date	Region	No. of cases	Mother's age (years)	Trimester during examination	Concomitant disease	Symptoms	C-section	Apgar	Outcome- fetuses/ newborns	Prenatal complications	Transmission
Yangli Liu, 2020	08 Dec. 2019 – 25 Feb. 2020	(Zhejiang, Hubei, Fujian, Shanxi, Beijing, Guangdong, Jiangxi, Heilongjian, Anhui) Wuhan, China	13	22–36	3rd trim.	No relevant medical history	Fever – 77% Dyspnoea – 23% Fatigue Sore throat Cough	10/10	10	6/10 – premature labour	3/10 – fetal distress 1/10 – rupture of membranes 1/10 – stillbirth	No vertical transmission
Zhu H, 2020	Jan. 2020 – 05 Feb. 2020	5 hospitals in Hubei, China	9 (2 twins, 8 singelton; 10 newborns)	average 30	31–39 hbd; 3rd trim.	Not mentioned	Fever Cough Diarrhoea Sneezing Nasal congestion Sore throat	7/9	7–10 (7 points – 1 case)	4 – full-term 6 – preterm infants 2 – SGA 1 – LGA 1 – demise after delivery	6 –intrauterine distress 5 – rupture of membranes 2 – abnormal amniotic fluid 2 – abnormal umbilical cord 1 – abnormal placenta	2019-nCoV NAT returned negative results for all neonates
Chen H, 2020	Jan. 2020 – 31 Jan. 2020	Wuhan, China	9	26–40	36–39 + 4 hbd; 3rd trim.	1 – gestational hypertension 1 – pre-eclampsia	Fever – 78% Myalgia – 33% Malaise – 22% Cough – 44% Dyspnoea – 11% Sore throat – 22% Diarrhoea – 11%	9/9	8–10	4 – preterm 4 – < 2500 g birth weight	2 –intrauterine distress 2 – rupture of membranes	The presence of SARS-CoV-2 was tested in amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples collected from six patients Neither the Kit recommended by CDC nor our in-house nested RT-PCR assays detected SARS-CoV-2 in these samples

Table 1. Cont.

Author	Date	Region	No. of cases	Mother's age (years)	Trimester during examination	Concomitant disease	Symptoms	C-section	Apgar	Outcome- fetuses/ newborns	Prenatal complications	Transmission
Dehan Liu, 2020	20 Jan. 2020 – 10 Feb. 2020	Wuhan, China	15	23–40	12–38 hbd; Average 32 hbd; 1st–3rd trim.	1 – thalassemia and gestational diabetes 1 – mitral valve and tricuspid valve replacement 10 years earlier 1 – complete placenta previa	Fever – 13/15 Cough – 10/15 Fatigue – 4/15 Muscle ache – 3/15 Dyspnoea – 1/15 Sore throat – 1/15 Diarrhoea – 1/15	10/11	8–9	3 – preterm	–	–
Fan C, 2020	27 Jan. 2020 –14 Feb. 2020	Hubei, Shanghai, China	2	29–34	36–37 hbd; 3rd trim.	No relevant medical history	C1 – Fever, skin rush C2 – chill, fever, nasal congestion, sore throat	2/2	9–10	1 – preterm		SARS-CoV-2 was not detected in all the products of conception and the infants
Nan Yu, 2020	1 Jan. 2020 – 08 Feb. 2020	Wuhan, China	7	29–34; Average 32	37–41 + 2 hbd	1 – hypothyroidism 1 – polycystic ovary syndrome 3 – uterine scarring 1 – H1N1 coinfection 1 – Legionella pneumophila coinfection	6 – fever (86%) 1 – cough (14%) 1 – shortness of breath (14%) 1 – diarrhoea (14%)	7/7	8–10	–	–	Nucleic acid test for the throat swab of one neonate was positive at 36 h after birth
summary	Dec 2019 – Feb 2020	China	55 gravidas; 56 fetuses	22–40	1st–3rd trim.; Mostly 3rd trim.	Mostly healthy women, before infection	Non-characteristic symptoms	45/48; 93%	Mostly 8–10; 1 case 7	20/48 (41%) – preterm labour		No evidence of SARS-CoV-2 vertical transmission

trim. – trimester, C – case

Table 2. Ultrasound and echocardiographic markers of fetal viral infections

Virus	Ultrasound findings	Echocardiographic features which may indicate fetal viral infection
Rubella	• Obstetrics ultrasound: micrognathia, microcephaly, microphthalmos, bony radiolucencies, intra-uterine growth restriction, hepatomegaly, splenomegaly, calcification of placenta, liver, brain, spinal cord, eyes, kidneys, and musculoskeletal system, cleft lip, • Fetal echocardiography recommended	• Fetal cardiomegaly • Fetal heart hypertrophy • Pericardial effusion • Myocardial hypokinesis • Increased echogenicity of the valves • Increased echogenicity of endocardium • Bright spot or bright spots • Functional regurgitations (most often tricuspid valve regurgitation) • Ductus arteriosus constriction • Premature closure of the foramen ovale • Dilatation of the coronary arteries • Fetal heart arrhythmias • Tachycardia • Bradycardia
Cytomegalovirus (CMV)	• Obstetrics ultrasound: microcephaly, cerebellar aplasia, intra-uterine growth restriction, hydrops fetalis, ascites, periventricular calcifications, hydrocephalus, liver calcification, hepatomegaly, splenomegaly, retinal calcification, diffuse placental inflammation • Fetal echocardiography recommended	
Herpes simplex virus (HSV)	• Obstetrics ultrasound: intra-uterine growth restriction, hepatomegaly, microcephaly, periventricular and placental calcifications, microcephaly, hydrocephaly, cerebral atrophy • Fetal echocardiography recommended	
Parvovirus B19	• Obstetrics ultrasound: hydrops fetalis, oedematous skin, ascites, pleural effusion, hepatomegaly, splenomegaly, hydrocephaly, calcification of liver and spleen, eye abnormalities, anencephaly • Fetal echocardiography recommended	
Varicella zoster virus	• Obstetrics ultrasound: placental calcification, retinal and intracranial calcification, intra-uterine growth restriction, limb deformities, skin scarring, microcephaly, hepatomegaly, splenomegaly • Fetal echocardiography recommended	
Coxsackie viruses B1 and B5	• Obstetrics ultrasound: urogenital malformations, gastrointestinal malformations, central nervous system destruction- not associated with chromosomal anomalies or genetic syndromes • Fetal echocardiography recommended	
Influenza	• Obstetrics ultrasound: pneumonitis, pleural effusion, intra-uterine growth restriction • Fetal echocardiography recommended	

This statement is consistent with most common patients' symptoms: fever, cough, dyspnoea, etc. [1]. Our analysis showed that these symptoms are also present in pregnant women, who do not experience any other characteristic complaints. Diarrhoea affects approximately 3% of cases with COVID-19 in the general population [1]. However, Chen et al. noted a higher incidence in gravidas (11%) [5]. Any suspected case should be tested for SARS-CoV-2, using available tests, such as quantitative reverse transcription polymerase chain reaction (RT-PCR). In pregnant women a CT scan is essential not only for evaluation of the clinical condition, but also may be used as a primary tool for detection of COVID-19 in epidemic areas [12]. A chest CT scan of a COVID-19 patient shows characteristic features in the disease process in lungs and has high sensitivity and speed for diagnosis [13]. Adverse effects of radiation exposure (> 610 mGy) for fetuses are well-known, for example: fetal growth restriction, microcephaly, or intellectual disability [14], so a minimal number of CT scans, lead blankets on the lower abdomen and pelvis (uterus), and low-dose imaging mode should have been, and indeed were, used in the evaluated studies [6, 12].

Topical articles are focused on the maternal state but lack detailed fetal description. It is worth to discussing whether COVID-19 maternal infection should be indication for further, more specific fetal ultrasound. Scientists and experts agree that fetal monitoring should be conducted using ultrasonography [12, 14]. Ultrasound assessment of fetal growth, amniotic fluid volume, umbilical artery Doppler, and fetal heart rate should be checked [12, 14]. More advanced monitoring is recommended once the fetus reaches viability [14]. Other viral fetal infections co-occur with prenatal symptoms, which can be detected by ultrasonography (Table 2) [15–18]. Ye et al. presented a study suggesting that maternal viral infection is significantly associated with risk of congenital heart defect in offspring [19]. Viruses such as cytomegalovirus (CMV) and rubella virus can cause transplacental infection. Other viruses are occasionally able to gain access to the fetus via the hematogenous route. Herpes simplex virus (HSV), varicella zoster virus (VZV), and Coxsackievirus are among those that can cross the placental barrier and infect the fetus [16]. Until now, no characteristic fetal symptoms of COVID-19 have been described. Moreover, there are no data showing that SARS-CoV-2 is able to cross the feto-maternal protective barrier and cause fetal viraemia, and no evidence of SARS-CoV-2 vertical transmission was found in the analysed manuscripts [5–10]. However, we have to re-

Table 3. Routine elements of fetal echocardiographic examination

	Additional fetal echocardiography elements
Separate elements of examination	Time of examination: > 45 min, about 1–1.5 h Techniques: colour Doppler, spectral Doppler, power Doppler, power angio, M-Mode, tissue M-Mode, 3D, 4D Detailed examination of: atria, ventricles, foramen ovale and its flap, valves: mitral, tricuspid, aortic, pulmonary, pulmonary trunk, aortic arch, isthmus, descending aorta, pulmonary arteries, superior vena cava, inferior vena cava, intraventricular septum, ductus venosus, ductus arteriosus, umbilical arteries and vein, upper mediastinum, thymus Parameters: AP (transverse heart diameter), shortening fraction, TEI index, Pulsatility index, Resistance index, TAPSE, MAPSE

member that maternal viral infections do not need to bypass the placental barrier to affect fetal development [20]. According the guidance, suspected, probable, or confirmed cases of COVID-19 should be managed by tertiary hospitals [12]. These recommendations preserve the unpredictable COVID-19 course in pregnant women and enable, from the logistic point of view, more complex perinatal care. At this point the authors would like to highlight the special importance of fetal heart and cardiovascular system examination. One of the methods of fetal monitoring is targeted echocardiography, which, with high probability, predicts normal fetal development before and after delivery [21]. Fetal echocardiographic examination contains basic obstetrical screening in addition to elaborate cardiovascular assessment (Table 3) [22]. This examination requires direct contact between the patient and an experienced echocardiographer and lasts at least 45 min [22]. Basic obstetric screening (15–20-min scan) might detect major congenital anomalies, both cardiac and extracardiac. Detection of subtle sonographic findings is dedicated for echocardiography and requires more time and more experience. Rimmer et al. contraindicate, for

Table 4. Indications for emergency fetal echocardiography during the COVID-19 pandemic

Major indications for fetal echocardiography
Congenital heart defect or extracardiac defect
Fetal ascites or hydrothorax or severe pericardial effusion (> 5 mm)
Fetal heart arrhythmias (FHR > 180 beats/min and < 100 beats/min)
Twin pregnancy with asymmetric twins > 25%

Table 5. Polish Registry for Fetal Cardiac Malformations www.orpkp.pl for 2020-2021

Aims of orpkp.pl for years 2020–2021
Any differences in the number of affected fetuses in comparison with 2018–2019?
Any differences in types of heart defects, arrhythmias, or other problems?
Any differences in premature deliveries?
Any differences in caesarean sections versus vaginal deliveries?
Any differences in geographic areas for clusters of heart defects?

women (medical workers: doctors, nurses, etc.) who are more than 28 weeks pregnant, direct contact with patients, in order not to be infected [23]. Considering the pandemic state, should also prenatal echocardiographers limit their examination only to basic measurements or totally confine their work? It may occur that more detailed analysis is impossible. In the authors' department, which is part of a Polish tertiary centre for pregnant women, in the era of the COVID-19 pandemic, full examinations are provided for special cases, due to limited human resources and other emergent reasons. Currently we have four major indications for fetal echocardiography (Table 4): congenital heart defect or extracardiac defect (as fetal heart will tell us about the fetal condition and its short-term and long-term prognosis); fetal ascites or hydrothorax or severe pericardial effusion (> 5 mm); fetal heart arrhythmias (FHR > 180/min and < 100 beats/min), and twin pregnancy with asymmetric twins > 25%. Presumably, the impact of SARS-CoV-2 on fetal life will be better understood in a few years, after a series of tests (echocardiography, eye test, hearing test, psychological evaluation, etc.), not among fetuses, but among infants, children, and adolescents. Here arises the probable need for further tertiary monitoring of newborns touched by maternal SARS-CoV-2 infection. For now, the prognosis for fetuses whose mothers were infected with SARS-CoV-2 is good, but still there are too few data, and, as we know, prenatal viral infections might be connected with poor outcome [24]. To date, COVID-19 concerns mainly the third trimester. First and second trimester infection is a current problem, which is growing before us. Further studies with postnatal follow-ups are needed because as yet there are no available data.

COVID-19 itself is not an indication for special delivery timing and mode, unless there are maternal indications like persistent hypoxia requiring improvement [12]. A high rate of C-section deliveries was noted (93%), but the reason was not provided in all studies. Di Mascio et al. also noted higher rate of caesarean sections among COVID-19 pregnant women than in the general population [25]. In the case of COVID-19 there is no clear benefit of C-section, and treatment during pregnancy should be profoundly deliberated [14].

In the era of COVID-19 the Polish National Registry for Cardiac Problems (www.orpkp.pl) [26] is of special value, operating under the auspices of the Polish Prenatal Cardiology Society. Al-

though this registry (existing for the last 15 years) is not obligatory, it could be a good source of data from the obstetricians and fetal cardiologists in our country, who would devote their efforts and time to share their cases with us for future analysis. Together, we could answer unsolved questions (Table 5). In the time of COVID-19 the Tricefy4 company is offering hospitals around the world the possibility to join efforts and communication via the cloud. Their program is excellent and worthy of strong recommendation from our side, because the Department of Prenatal Cardiology of the Polish Mother's Memorial Hospital, Research Institute in Lodz is the first Polish user of this program in our country. Communication via internet and medical consultations of fetal heart movies were never so easy and clear.

Conclusions

The authors present data from a literature research of pregnant women infected by SARS-CoV-2. COVID-19 pregnant women should be managed with special concern because maternal infection is known to have influenced maternofetal well-being in previous pandemics. The current literature does not allow for more precise description of fetal functional changes in the course of maternal COVID-19. More extensive studies are needed with special consideration of fetal cardiovascular system examination and further postnatal monitoring and more extensive epidemiological evaluation.

Conflict of interest

The authors declare no conflict of interest.

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