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Complications in Pregnancy in COVID-19 Positive Women

Linn Stenberg[1]*; Micaela Veneziano[2]; Donatella Mascheroni[3]; Matteo Bonatti[4]; Federica Verdi[2]; Monica Braghetto[2]; Jana Žodžika[5]; Martin Steinkasserer[2]

[1]Rīga Stradiņš University, Faculty of Medicine, Riga, Latvia.

[2]Department of Obstetrics and Gynecology, Provincial Hospital of Bolzano, Bolzano, Italy.

[3]Department of Neonatology and Neonatal Intensive Care, Provincial Hospital of Bolzano, Bolzano, Italy.

[4]Department of Radiology, Provincial Hospital of Bolzano, Bolzano, Italy.

[5]Rīga Stradiņš University, Faculty of Medicine, Department of Obstetrics and Gynecology, Riga, Latvia.

***Corresponding Author(s): Linn Stenberg**

Rīga Stradiņš University, Faculty of Medicine Riga, Latvia.

Tel: +46-73-388-87-89; Email: linnsofc@gmail.com

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Keywords: COVID-19; Pregnancy; Complications; Vertical transmission; Infection.

Key message: Clinical presentation of COVID-19 infected pregnant women is variable, from asymptomatic or mild symptoms with spontaneous recovery to interstitial pneumonia requiring intensive care, mechanical ventilation and antiviral therapy.

Abstract

Introduction: As observed in two Coronavirus epidemics in the past, pregnant women seem to be particularly vulnerable for virus infections and severe clinical outcomes. We retrospectively analysed all complications and their outcome in pregnant women with laboratory confirmed COVID-19 infection admitted to the Provincial Hospital of Bolzano in northern Italy during Corona emergency between 27th February and 27th April 2020.

Patients and methods: 12 pregnant patients with a median age of 33 years (SD + 6.2) were included in this retrospective observational study. All patients were admitted to the Department of Obstetrics and Gynecology during Corona emergency. Of the 12 patients all clinical records, laboratory data and available CT scans or chest X-rays were recorded and evaluated. All newborns underwent nasopharyngeal swab for RT-PCR testing.

Results: Nine of the 12 patients (75%) showed symptoms of a COVID -19 infection, 3/12 (25%) were asyptomatic. Six of 12 (50%) presented with cough, 5 (41.6%) had also dispnea and fever before and/or after delivery. Other symptoms were malaise, rhinitis and flu-like bone pain. Six of 12 patients (50%) developed interstitial pneumonia verified by CT scan or X-ray.

Six patients (50%) had pregnancy related complications (diabetes type I and obesity, polyhydramnion, anhydramnion, fetal distress and PROM/placental abruption, stress asthma). Two patients had to undergo C-section due to symptoms deterioration, 3 due to fetal distress and one due to a placental abruption.

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Although all newborns were tested negative for COVID-19 at the RT-PCR test, one newborn showed severe COVID-19 related symptoms. COVID-19 testing was negative in all placentas.

Conclusion: The clinical presentation of COVID-19 infected pregnant women in the present study was variable, from asymptomatic or mild symptoms with spontaneous recovery to interstitial pneumonia requiring intensive care, mechanical ventilation and antiviral therapy. Patients without risk factors during pregnancy did not seem to have a worse devolution of the disease. Thus, patients with risk factors like obesity, diabetes mellitus or hypertension develop a life-threatening disease presentation and vertical transmission seems to happen. Coronavirus infected pregnant women with severe symptoms seem to be at risk of negative obstetrical outcome with relatively higher preterm problems and C-sections.

Introduction

On March 11, 2020 after spreading around the globe for months, the novel coronavirus SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO). Incidence figures are steadily increasing, many of which manifest with a severe course affecting sensitive organs such as the lungs and kidneys. Up to date over 23 million cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have been confirmed globally, with a constantly rising number. More than 780,000 deaths worldwide have also been confirmed, resulting in a mortality rate of about 3.6% [1].

Italy was the first European country to be hit full on by the pandemic with over 259,000 cases and over 35,000 deaths [1] and was under lock down from 10th March till 4th May 2020. This paper is focusing on the situation in the Province of Bolzano in the very north of Italy and in particular on the main Provincial Hospital of Bolzano which has a basin of 220,000 people. In this province, today (24.08.2020) 2,869 cases and 292 deaths were counted.

Several risk groups for a severe course of the disease have been identified. These include the elderly, people with respiratory diseases and immunocompromised persons as well as pregnant women. All of the mentioned belong to the risk category I.

The higher risk in pregnant women is based on the fact that during pregnancy the immune system is weakened due to exposure to fetal antigens [2]. Besides the novel Coronavirus it has been known previously that Influenza A, Middle East Respiratory Syndrome (MERS) and other coronaviruses can have a more severe disease progression and might have severe negative consequences on pregnancy [3].

The aim of the study was the retrospective collection and analyses of detailed clinical data from the complete records and follow up visits in the outpatient clinic from pregnant women with laboratory confirmed COVID-19 infection and the documentation of all complications and their outcome at the Provincial Hospital of Bolzano. Furthermore, we analyzed whether COVID-19 positivity leads to a changed birth process and vertical transmission.

Patients and methods

12 Pregnant patients with a median age of 33 years (SD + 6.2) were included in this retrospective cohort observational study at the Department of Gynecology and Obstetrics at the Provincial Hospital of Bolzano (ethical approval 47-2020). All patients were admitted to the department during Corona emergency between 27th February and 27th April 2020 and had a positive real time polymerase chain reaction (RT-PCR) test for SARS-CoV-19 RNA (on two throat or nose swabs). Of the 12 patients all clinical records, laboratory data and available CT scans or chest X-rays were recorded and evaluated. Eight out of 12 patients were in their 3rd trimester (35th-39th week), 4/12 in their second trimester (between 20th and 27th week).

All patients, who were admitted to the department, were followed according to a protocol elaborated by a multidisciplinary team, composed of gynecologists, neonatologists, nurses and obstetricians, anesthesiologists, and with the telephone consultation of the Serology (Microbiology Laboratory) and the Infectious Diseases Department (on-call consultant) taking into account the scientific and epidemiological data available and on the basis of the Guidelines published in the Lombardy Region [4].

All the newborn were swabbed for COVID-19.

Statistical analysis

Since this was an observational study, no hypothesis could be generated without bias. It was not about proof of an assumption, but about observation and description of previously unknown phenomena.

The size of the study was not predictable. All patients who were positive and pregnant during the study period of COVID-19 and who were cared for at the Bolzano hospital were included. The sample size was so small that it was limited to only one case series, the scientific presentation was to be made in a case report.

Ethical approval

The study was approved by the local Ethical Committee on 14th May 2020 with approval number 47/2020.

Results

Eleven of 12 patients resulted positive for COVID -19. One test was not diagnostic and was not repeated. The patient had COVID-19 symptoms and showed a positive IgG blood test later on.

Five (41.6%) patients had a COVID-19 sick family member, 2 of them had also contact with a COVID - 19 positive midwife.

Nine of the 12 patients (75%) showed symptoms of a COVID-19 infection, 3/12 (25%) were asymptomatic. Five of the 12 patients (41.6%) had fever before and/or after delivery. Six of 12 (50%) presented with cough, 5 (41.6%) had also dyspnea. Other symptoms were malaise, rhinitis and flu-like bone pain. None of the patients had sore throat or diarrhea. Six of 12 patients (50%) developed interstitial pneumonia verified by CT scan or X-ray. 1/12 did not show the typical picture of COVID -19 related pneumonia at the X-ray despite having symptoms related to the virus. One patient developed additional bilateral pleural effusions (Figure 1 & 2). This patient had to be intubated and developed successively sepsis and ketoacidosis. The other 5 patients needed oxygen support. All patients were treated

with antithrombotic therapy, 4 also with antiviral/antimalarial therapy (Kaletra and Plaquenil). One was treated additionally with Azithromycin and Remdesevir. Nine of 12 patients (75%) underwent antibiotic therapy, 3 (25%) were treated additionally with corticosteroids.

Eleven of 12 (91.6%) patients showed low or normal white blood cell count between 3.24 and 9.11x1000 cells/µl, one had an elevated count (13.49x1000cells/µl). Five of 12 (41.6%) patients had lymphopenia ranging between 0.33 and 1.05x1000 cells/µl. C-reactive protein was elevated in 6 (50%) patients (1.2-8.16 mg/dl). In 2 patients C-reactive protein was below 0.5 mg/dl and in 4 patients it was not tested. ALT was normal < 35 U/L in 11 of 12 patients, one patient had ALT 111 U/L, AST was elevated in 2 patients (40 and 47 U/L).

Six of 12 patients (50%) delivered spontaneously, 6 (50%) underwent a C-section. Two patients had to undergo C-section due to symptoms deterioration, 3 due to fetal distress and one due to a placental abruption. Five patients did not show any pregnancy related risk factors or complications. Six patients had pregnancy related complications (diabetes type I and obesity, polyhydramnion, anhydramnion, fetal distress and PROM/placental abruption, stress asthma).

Although all newborns were tested negative for COVID-19 at the RT-PCR test, one newborn showed severe COVID-19 related symptoms. COVID-19 testing was negative in all placentas. Detailed data are summarized in Tables 1-3.

Figure 1: Chest CT scan acquired in the acute phase shows multiple bilateral parenchymal consolidations and ground-glass opacities that prevalently affect the lower lobes. Bilateral pleural effusion is also present.

Figure 2: High resolution chest CT scan acquired 3 months after clinical recovery shows no opacities or septal thickenings. No pleural effusion.

Table 1: Clinical and laboratory characteristics of patients [1-6].

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Clinical characteristics						
Date of admission	13.03.20	25.03.20	19.03.20	17.03.20	19.03.20	27.02.20
Age	27	39	37	19	36	38
Gestational week on admission	36th week+2	38th week+2	39th week	38th week+2	35th week+1	20th / delivery 32nd week+1
Epidemiology/contact COVID19 +		Husband/mother		Husband/midwife		
Complications in pregnancy	diabetes type I	polyhydramnion	fetal distress	respiratory	anhydramnion	PROM/placental
	obesity			problems		abruption
Signs and symptoms						
Fever on admission	yes	yes	yes	no	no	no
Post-partum fever	yes	yes	yes	yes	no	no
Rhinitis	no	no	no	no	no	no
Malaise	no	no	yes	no	no	no
Bone pain	no	no	yes	no	no	no
Cough	no	yes	yes	yes	no	no
Dyspnoea	yes	yes	yes	yes	no	no

Sore throat	no	no	no	no	no	no
Diarrhea	no	no	no	no	no	no
Interstitial pneumonia	yes	yes	no	yes	no	no
Laboratory characteristics						
White blood cell count (x1000 cells/µl)	6.22	5.34	7.6	5.62	7.73	7.43
Low or normal leucocyte count	yes	yes	yes	yes	yes	yes
(<9.5x1000 cells/µl)						
Lymphocyte count (x1000 cells/µl)	0.33	1.04	0.93	1.18	2.32	1.50
Lymphopenia (x1000 cells/µl)	yes	yes	yes	no	no	no
C-reactive protein concentration (mg/dl)	8.16	2.23	1.69	1.93	n.p.	0.24
Elevated C-reactive protein (>0.5 mg/dl)	yes	yes	yes	yes	n.p.	no
Elevated ALT (>35U/L) or AST (>35U/L)	no	yes	no	no	no	no
ALT (U/L)	17	111	23	16	20	14
AST (U/L)	26	47	14	12	12	7
Confirmatory test done (SARS-CoV-2	yes	yes	yes	yes	yes	yes
quantitative RT-PCR)						
CT/Rx evidence pneumonia						
Typical signs of viral infection	yes	yes	no	yes	no	no
Delivery						
Method of delivery	C-section	C-section	C-section	spontaneous	C-section	C-section
Indication for C-section	symptoms	symptoms	Fetal distress		oligohydramnion	Placental
	deterioration	deterioration			Fetal distress	abruption
Treatment after delivery						
Oxygen support (nasal canula)	yes	yes	yes	yes	no	no
Antiviral therapy	yes	yes	no	no	no	no
Antibiotic therapy	yes	no	yes	yes	yes	yes
Antithrombotic therapy	yes	yes	yes	yes	yes	yes
Use of corticosteroid	no	no	yes	no	no	yes
Newborn						
Confirmatory test done (SARS-CoV-2	negative	negative	negative	negative	negative	negative
quantitative RT-PCR)						

Table 2: Clinical and laboratory characteristics of patients [7-12].

	Patient 7	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**
Clinical characteristics						
Date of admission	24.04.20	27.04.20	01.04.20	27.03.20	19.03.20	15.03.20
Age	38	25	35	30	30	31
Gestational week on admission	38th+1	37th week+4	20th week	27th+5	23rd+6	37th
Epidemiology/contact COVID19 +	father in ICU	no	husband	no	no	Husband/midwife
Complications in pregnancy	no	no	no	Stress astma/antima-laric first 3rd	no	no
Signs and symptoms						
Fever on admission	no	no	no	yes	no	no
Post-partum fever	no	no	no	yes	no	no
Rhinitis	no	no	yes	no	yes	no
Malaise	no	yes	yes	no	yes	no
Bone pain	no	no	no	no	no	yes
Cough	no	yes	no	yes	no	yes

Dyspnoea	no	no	no	yes	no	no
Sore throat	no	no	no	no	no	no
Diarrhoa	no	no	no	no	no	no
Interstitial pneumonia	no	yes	no	yes	no	no
Laboratory characteristics						
White blood cell count (x1000 cells/µl)	7.78	7.18	8.55	3.24	8.50	13.49
Low or normal leucocyte count	yes	yes	yes	yes	yes	no
Lymphocyte count (x1000 cells/µl)	3.9	1.25	2.17	0.65	1.7	1.05
Lymphopenia (x1000 cells/µl)	no	no	no	yes	no	yes
C-reactive protein concentration (mg/dl)	n.p.	2.35	n.p.	1.2	0.29	n.p.
Elevated C-reactive protein (>0,5 mg/dl)	n.p.	yes	n.p.	yes	no	n.p.
Elevated ALT (>45U/L) or AST (>35U/L)	no	yes	no	no	no	no
ALT (U/L)	15	32	7	10	18	5
AST (U/L)	8	40	12	14	14	12
Confirmatory test done (SARS-CoV-2	yes	yes	yes	yes	yes	not diagnostic
quantitative RT-PCR)						IgG positive
CT/Rx evidence pneumonia						
Typical signs of viral infection	n.p.	yes	no	yes	no	no
Delivery						
Method of delivery	spontaneous	spontaneous	spontaneous	spontaneous	spontaneous	C-section
Indication for C-section						Fetal distress
Treatment after delivery						
Oxygen support (nasal canula)	no	no	no	yes	no	no
Antiviral therapy	no	yes	no	yes	no	no
Antibiotic therapy	no	no	no	no	no	yes
Antithrobotic therapy	yes	yes	no	yes	no	yes
Use of corticosteroid	no	no	no	no	no	yes
Newborn						
Confirmatory test done (SARS-CoV-2	negative	negative	negative	negative	negative	negative
quantitative RT-PCR)						

Table 3: COVID -19 associated complications in patients.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Interstitial pneumonia	yes	yes	yes (not typical for COVID)	yes	no	no
Pleural effusion	yes	no	no	no	no	no
Sepsis	yes	no	no	no	no	no
Ketoazidosis	yes	no	no	no	no	no
Transmission to the newborn	yes	no	no	no	no	no
	Patient 7	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**	**Patient 12**
Complications						
Interstitial pneumonia	no	yes	no	yes	no	no
Pleural effusion	no	no	no	no	no	no
Sepsis	no	no	no	no	no	no
Ketoazidosis	yes	no	no	no	no	no
Transmission to the newborn	no	no	no	no	no	no

Discussion

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by the novel COVID-19 disease is a highly infectious disease, with its ongoing outbreak being declared a global public health emergency on 11.03.2020 by WHO [5,6]. The main epidemiological risk factors seem to be age above ~55-60 years, diabetes, hypertension, morbid obesity, chronic kidney disease, coronary artery disease, heart failure, chronic pulmonary disease, transplants or other forms of immunosuppression and HIV [7].

As we have learned from two large Corona Virus epidemics in the last years, the Severe Acute Respiratory Syndrome Corona Virus 1 (SARS-CoV-1) and the Middle East Respiratory Syndrome (MERS), it seems that pregnant women are particularly vulnerable for virus infections and severe clinical outcomes [8,9]. Physiological, anatomical and alterations in cell-mediated immunity seem to lead to an increased susceptibility of pregnant women to be infected by intracellular organisms like viruses [10-12]. Previous studies reported that SARS, MERS and H1N1 in pregnancy led to serious illness and to higher mortality rates [13]. Even though the opinions about susceptibility of pregnant women to Coronavirus infection are discordant, it was observed that at least 20% of patients developed severe or critical infections [14]. Thus, the most reported COVID-19 infections during pregnancy are asymptomatic or manifest with mild pneumonia and are similar to symptoms in non-pregnant adults [10]. In infected pregnant women fetal distress and preterm delivery were seen in some cases [15]. There are only few data on SARS and MERS in pregnancy. For SARS the largest series report on 12 cases with a fatality rate of 25%. The mechanical ventilation rate was in pregnant women three times higher than in non-pregnant women. Very similar is the fatality rate in MERS-CoV infected pregnant women with 23%. However, also here only 13 cases were reported [16].

This is a retrospective, observational study on 12 pregnant women who were admitted to the department of Obstetrics and Gynecology of the Provincial Hospital of Bolzano between 27th February and 27th April 2020 during the first Italian Corona lock down. Eight patients were in their 3rd trimester, 4 in their 2nd. Eleven of 12 patients were tested positive for COVID-19, one test was not diagnostic. The patient was later IgG positive. Three patients (25%) were asymptomatic, 9 of the 12 patients (75%) showed COVID-19 symptoms. Of the 9 patients, 4 (33%) showed mild flu-like symptoms like malaise, rhinitis, bone pain but also cough and dyspnea. This is in accordance with the data reported by Chen et al [10] who describes that the most common symptoms for the mild COVID-19 infection are the ones mentioned above. However, 5 (41.6%) of the 12 patients developed an interstitial pneumonia accompanied by fever. Liu et al reported that some patients recovered from COVID-19 pneumonia despite not being treated with antiviral therapy [17]. This was observed also in our patient´s cohort. In fact, 2 of 5 patients recovered from pneumonia without being treated with antiviral therapy. Two patients recovered after antiviral therapy with Plaquenil and Kaletra. One patient progressed to ARDS with respiratory failure so that she had to be transferred to ICU, intubated and was mechanical ventilated. In addition to a severe interstitial pneumonia, this patient had also bilateral pleural effusions and sepsis. She was treated with Plaquenil, Kaletra, Azytromyzin and Remdesevir. She had 2 major risk factors for severe COVID-19 infection, severe obesity and diabetes mellitus type I. The patient developed furthermore ketoacidosis after extubation and had to be reintubated. The newborn showed severe COVID-19 symptoms. A similar case with diabetes mellitus type 2 and progression to respiratory failure was described by Alzamora et al. [18]. Breslin et al [14] reported 2 cases of pregnant patients with obesity and poorly controlled diabetes mellitus who had also to be admitted to ICU due to progress to respiratory failure. Considering these observations, severe maternal morbidity cannot be excluded with COVID-19 infection during pregnancy.

The main laboratory findings were elevated C-reactive protein in 6/12 (50%) patients and lymphopenia in 5/12 patients (41.6%). In our cohort, both abnormalities were related to a more severe infection and pneumonia in most cases. Previous studies [10,17] also reported lymphopenia and elevated C-reactive protein as most common laboratory findings. They were, however, not necessarily related to COVID-pneumonia. Chen et al. [10] also suggested that increased levels of ALT and AST might be one of the clinical manifestations, although in his study cohort none of the patients showed elevated concentrations. In our study group, one patient showed elevated ALT levels and 2 patients elevated AST levels. All patients with elevated C-reacted protein, elevated ALT/AST and lymphopenia in our study group had a CT/Rx confirmed pneumonia.

Of the 12 patients, 6 underwent C-section due to symptoms deterioration or fetal distress. One woman had a placental abruption. Chen et al [10] reported that premature birth was not related to COVID pneumonia. In contrast, Di Mascio et al [16] reported in a systematic review that hospitalized Coronavirus infected women are at increased risk of severe outcomes and that especially COVID-19 infected women had higher rates of preterm birth and C-sections.

All 12 newborns had a negative COVID-19 RT-PCR Test. Nevertheless, one baby showed severe COVID symptoms. The babyboy was admitted to neonatal ICU for mild hyaline membrane disease, hypoglycemia, polyglobulinemia and preterm bradycardia crisis.

As previously mentioned, COVID-19 testing was negative in all placentas. This is in accordance with the previously published data by Chen et al [10], Di Mascio et al [16], Zhu et al [19] and Zaigham and Anderson [3] who all reported none or minimal rate of vertical transmission of the infection on the baby. They also suggested that COVID-19 may have negative impact on the babies causing fetal distress, premature labour or respiratory distress. Therefore, Zhu et al suggest a systematic screening during pregnancy. At the moment it is unknown if COVID can be transmitted from mother-to-foetus. Due to the missing knowledge it seems reasonable to assume that the newborn born to a mother with COVID-19 could be infected during labour or in utero. Thus, the newborn should be isolated to avoid infecting other newborns. It is actually recommended to separate temporarily the ill mother from her newborn. [15].

Conclusion

The clinical presentation of COVID-19 infected pregnant women in the present study was variable, from asymptomatic or mild symptoms with spontaneous recovery to interstitial pneumonia requiring intensive care, mechanical ventilation and antiviral therapy. Patients without risk factors during pregnancy did not seem to have a worse outcome of the disease. Thus, patients with risk factors like obesity, diabetes mellitus or hypertension develop a life-threatening disease presentation and

vertical transmission seems to happen. Coronavirus infected pregnant women with severe symptoms seem to be at risk of negative obstetrical outcome with relatively higher preterm problems and C-sections.

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