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Case Report

COVID-19 and Pregnancy: An Unusual Case with Multi-Systemic Failure

Barta A[1], Cheron AC[1], Christophe JL[2], Doucet F[1] and Hubinont C[3*]

[1]Department of Obstetrics & Gynaecology, Grand Hôpital de Charleroi-Nôtre Dame, Charleroi, Belgium
[2]Department of Nephrology, Grand Hôpital de Charleroi, Charleroi, Belgium
[3]Department of Obstetrics, Cliniques Universitaires Saint Luc, Brussels, Belgium

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ABSTRACT

In December 2019, a new strain of coronavirus, SARS-CoV-2, was discovered in Wuhan and quickly became responsible for a worldwide pandemic. The first case reports of COVID-19 in pregnant patients are reassuring and no severe maternal-fetal complications have been reported. We present a case of SARS-CoV-2 infection during pregnancy presenting with renal and liver failure, suggesting similarity with pregnancy related HELLP syndrome and gestational cholestasis.

Introduction

The first cases of SARS-CoV-2 infection were reported in Wuhan, China, in December 2019. The virus spread quickly to other Asian countries as well as the rest of the world, leading to a worldwide pandemic. The human to human transmission is mainly due to droplets, but oral-fecal transmission is also possible. The median incubation period is 5.1 days and 97.5% of infected patients will have developed the disease within 11.5 days [1]. The main symptoms are fever, shortness of breath, coughing but also anosmia, myalgia, sore throat and gastrointestinal symptoms (vomiting, diarrhea and abdominal pain) were reported. Many cases were asymptomatic. Severe cases with respiratory distress could worsen quickly into multiple organ failure. Data about the impact of COVID-19 on pregnancy are spare and mostly based on small single centered retrospective studies.

Pregnant women are not more symptomatic compared to non-pregnant women. There is no clear evidence of vertical intrauterine transmission or through breastmilk [2]. Few cases of a positive throat swab in newborns are reported, but it appeared that it could be related to postnatal transmission [3, 4]. Pregnant women with COVID-19 are more likely to deliver prematurely and by caesarean section, secondary to inflammation and infection process. In conclusion, there is no evidence that COVID-19 causes severe maternal and neonatal complications among pregnant women [5, 6]. We present the case of a SARS-CoV-2 infection affecting a 31 weeks pregnant patient presenting with hepatic cytolysis, cholestasis and mild kidney failure.

Case Presentation

A 31-week primigravid 43-year-old woman consulted our department for a persisting cough, shortness of breath and fever. There was no chest pain and no sign of deep vein thrombosis. She had no medical issues except obesity, gestational diabetes and gastroesophageal reflux treated

Correspondence to: Corinne Hubinont, M.D., Ph.D., Department of Obstetrics, Cliniques Universitaires Saint Luc, Brussels, Belgium; E-mail: corinne.hubinont@uclouvain.be

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with insulin and omeprazole. At clinical examination, she was dyspneic at rest without cyanosis. She showed tachycardia (125 bpm) and tachypnea (28 per minute). She had a normal blood pressure of 123/72 mmHg. Her oxygen saturation level was between 92 and 97%. She had no fever. Arterial blood gas indicated respiratory alkalosis (pH 7.47, low pCO_2 at 21.8 mmHg, low HCO_3 at 15.7 mmol/l, normal SaO_2- and pO_2 levels) and an elevation of lactate level (2.02 mmol/l). A chest x-ray was performed and showed no sign of pneumonia nor other pulmonary disease. A nasopharyngeal swab for PCR-SARS-CoV-2 detection returned positive and a diagnosis of mild SARS-CoV-2 respiratory disease was retained.

Blood tests revealed an inflammatory syndrome (CRP at 62 mg/l and leucocytes at 12800/mm^3, 86.3 % of neutrophils and 9.3% lymphocytes), hepatic cytolysis (GOT 354, GPT 166, GGT 510 U/L), high LDH at 659 U/L, normal bilirubin level and a slightly elevated creatinine level (0.90 mg/dl). Hemoglobin and platelets level were in the normal range. A urine spot showed mild proteinuria (20 mg/dl). A cardiotocogram showed a normal fetal heart monitoring with no sign of fetal distress, and there were no uterine contractions. The fetal ultrasound was normal. Hydroxychloroquine treatment was started following the local protocol (2x200mg twice a day during the first 24h, 200mg twice a day for 4 more days), after an ECG ruled out Long QT syndrome. The patient was admitted with intensive monitoring of maternal and fetal parameters and oxygen administration. Corticosteroids (12mg of betamethasone twice, 24 hours apart) were administered for improving fetal lung maturity.

The patient's respiratory outcome was good, with occasional oxygen support. However, after a few days, blood tests showed an increase in ALT, AST and GGT (up to 524, 382 and 774 U/L respectively), total and direct bilirubin (up to 2.24 and 1.97 mg/dl, respectively), uric acid (up to 9.2 mg/dl) and CRP (up to 81mg/l). Creatinine started to rise (up to 1 mg/dl) and platelets level remained normal. Preeclampsia with Hemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome was suspected as the patient was a 43-year-old primiparous obese woman. However, she was not hypertensive but had a proteinuria of 555 mg/24h. The preeclampsia predicting test using sflt1/PIGF ratio was found positive at 155.62 (a ratio > 38 predicts a possible preeclampsia within the next 4 weeks; a ratio <38 predicts no preeclampsia in the next week). Auto-immune and other infectious hepatitis were ruled out. Liver ultrasound showed steatosis without any hepatic or biliary duct abnormalities. As hydroxychloroquine hepatotoxicity has been described, the treatment was stopped on day 4 [7].

As fasting biliary acids were elevated at 67.2 µmol/l (normal < 10 µmol/l), ursodeoxycholic acid was initiated 6 days after admission (15mg/kg/day). As the biological parameters improved, the patient was discharged 11 days after admission. There was a decrease in hepatic cytolysis (GOT 105 and GPT 183 U/L) with high bilirubin level (2.24 total bilirubin and 1.97 mg/dl direct bilirubin). The creatinine level remained stable at 1 mg/dl with uric acid at 8 mg/dl. CRP level was close to normal. She came back 4 days later for a routine antenatal visit and blood tests control showed an acute renal failure with a creatinine level of 1.4 mg/dl and an increase of urea and uric acid concentrations. Liver enzymes remained normal, but biliary acids were dramatically increased (490 µmol/l).

After multidisciplinary discussion with the neonatologists, obstetricians and nephrologists, induction of labor was decided at 34 weeks. After a normal vaginal labor, a eutrophic healthy newborn was delivered with an Apgar score of 8-8-9. The placenta was sent to pathology after delivery and showed an overall "vascular placenta" pattern with presence of a small retroplacental hematoma with a zone of infarction nearby. After delivery, blood pressure raised up to 160/100 mmHg and was treated by alpha-methyldopa (250 mg 3 times a day). Platelet count dropped transitory to 102.000/mm^3 on day 2. Creatinine level and liver enzymes and biliary acids went back to normal within a few days. She was discharged 4 days after delivery with an outpatient follow up with the general practitioner and the nephrologist.

Discussion

Our first case of SARS-CoV-2 infection in a pregnant patient had a different clinical pattern than those with pneumonia reported by the Chinese experience [3, 5]. Elevations of liver enzymes (ALT and AST), total bilirubin, heart enzymes (creatinine kinase and lactate dehydrogenase) and renal damage (elevation of seric urea and creatinine) have been described [8]. Mechanisms for liver damage in COVID-19 infection are unclear. It could be due to the virus itself and to the expression of Angiotensin-Converting Enzyme 2 (ACE2), which acts as a receptor of the virus in cholangiocytes [9]. It might also result from a hyperactivated immune response and cytokine storm related systemic inflammation that can affect and damage any organ [9]. Another possible explanation is the frequent use of paracetamol as an antipyretic drug or other antiviral therapies. Last but not least, COVID-19 could act as a trigger on a pre-existing liver disease [9]. The very high concentration of biliary acids was one of our main concerns. When they exceed 40 µmol/l, perinatal death risk increases significantly and over 100 µmol/l, a poor perinatal outcome is expected [10].

In our case, we suspected the SARS-CoV-2 infection to be responsible for the cholestasis rather than intrahepatic cholestasis of pregnancy as there was a rapid and significant increase despite ursodeoxycholic acid treatment. Our patient was admitted for Acute Renal Failure (ARF), concerning 3-7% of in-patients infected by SARS-CoV-2 and 4 times more common in patients in intensive Care Unit compared to non-intensive care units [11]. The physiopathology leading to ARF is complex and involves virus-mediated injury, cytokine storm, angiotensin II pathway activation, dysregulation of complement, hypercoagulation status and microangiopathy interacting with known risk factors for ARF. Direct infection of the kidney might also play a role [11, 12].

The main differential diagnosis of renal failure during pregnancy is preeclampsia. Placental vascular development relies on adequate balance between pro-angiogenic mediators (mainly vascular endothelial growth factor VEGF and Placental growth factor PIGF) and antiangiogenic mediators such as soluble fms-like tyrosine kinase (sflt-1). Most infections could induce a dysregulation of this balance through inflammatory mediators including cytokines e.g., interleukin 1, Interferon-γ, tumor necrosis factor and the complement system. sFlt1/PIGF ratio could also be modified by infectious states. Dysregulation of these mediators are associated with placental insufficiency, inadequate oxygen and nutrients delivery to the fetus,

leading to adverse birth outcomes [13]. The presence of placental hematoma in our case, confirms results from a recent study on placental pathology in COVID-19 positive pregnant patients. An increased prevalence of decidual arteriopathy and signs of maternal vascular malperfusion (MVM) was found, similar to those usually associated with hypertensive disease and preeclampsia [14]. One meta-analysis on COVID-19 and pregnancy also found an increased risk of preeclampsia in severely affected in-patients, but no data are available for less symptomatic pregnancies infected with SARS-CoV-2 [15].

Conclusion

SARS-CoV-2 infection is a multi-faceted disease that can mimic other pathologic conditions, including pregnancy-related diseases such as preeclampsia or intrahepatic cholestasis of pregnancy. Our case report highlights the difficulties for an appropriate diagnosis when facing COVID-19 in a pregnant woman. Differential diagnosis must be considered, and multidisciplinary management should be done according to actual guidelines. Large case studies on the impact of COVID-19 on pregnancy should be able to improve our knowledge and the maternal-fetal management of this infection.

Abbreviations

CRP: C-Reactive Protein
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
GGT: Gamma-glutamyltransferase
LDH: Lactate Dehydrogenase
ACE2: Angiotensin-Converting Enzyme 2
ARF: Acute Renal Failure
VEGF: Vascular Endothelial Growth Factor
PlGF: Placental Growth Factor
Sflt-1: Soluble Fms-Like Tyrosine Kinase
HELLP: Hemolysis Elevated Liver enzymes and Low Platelets
MVM: Maternal Vascular Malperfusion

Conflicts of Interest

None.

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References

1. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q et al. (2020) The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Internal Med* 172: 577-582. [Crossref]
2. Martins Filho PR, Santos VS, Santos HP Jr (2020) To breastfeed or not to breastfeed? Lack of evidence on the presence of SARS-CoV-2 in breastmilk of pregnant women with COVID-19. *Rev Panam Salud Publica* 44: e59. [Crossref]
3. Chen H, Guo J, Wang C, Luo F, Yu X et al. (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 395: 809-815. [Crossref]
4. Piersigilli F, Carkeek K, Hocq C, van Grambezen B, Hubinont C et al. (2020) COVID-19 in a 26-week preterm neonate. *Lancet Child Adolesc Health* 4: 476-478. [Crossref]
5. Li N, Han L, Peng M, Lv Y, Ouyang U et al. (2020) Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. *Clin Infect Dis* 352. [Crossref]
6. Hubinont C, Debiève F, Bernard P (2020) Grossesse et COVID-19. *Louvain Méd*.
7. Abdel Galil SM (2015) Hydroxychloroquine-induced toxic hepatitis in a patient with systemic lupus erythematosus: a case report. *Lupus* 24: 638-640. [Crossref]
8. Chen N, Zho M, Dong X, Qu J, Gong F et al. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395: 507-513. [Crossref]
9. Li J, Fan J (2020) Characteristics and Mechanism of Liver injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol* 8: 13-17. [Crossref]
10. Di Mascio D, Quist Nelson J, Riegel M, George B, Saccone G et al. (2019) Perinatal death by bile acid levels in intrahepatic cholestasis of pregnancy: a systematic review. *J Matern Fetal Neonatal Med* 19: 1-9. [Crossref]
11. Farkash EA, Wilson AM, Jentzen JM (2020) Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2. *J Am Soc Nephrol*. [Crossref]
12. Batlle D, Soler MJ, Sparks MA, Hiremath S, South AM et al. (2020) Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. *J Am Soc Nephrol* 31: 1380-1383. [Crossref]
13. Weckman AM, Ngai M, Wright J, McDonald CR Kain KC (2019) The Impact of Infection in Pregnancy on Placental Vascular Development and Adverse Birth Outcomes. *Front Microbiol* 10: 1924. [Crossref]
14. Shanes ED, Mithal LB, Otero S, Azad HA, Miller ES et al. (2020) Placental Pathology in COVID-19. *Am J Clin Pathol* 154: 23-32. [Crossref]
15. Mascio DD, Khalil A, Saccone G, Rizzo G, Buca D et al. (2020) Outcome of Coronavirus Spectrum Infections (SARS, MERS, COVID 1 -19) During Pregnancy: A Systematic Review and Meta-Analysis. *Am J Obstet Gynecol MFM* 2: 100107.