

DOI: <https://doi.org/10.30841/2708-8731.2.2023.278152>

UDC 618.3-578.834.1-616.155.194.18

# COVID-19 mimicked fetal hemolytic disease: a case report

**I. V. Lakhno**

Kharkiv National Medical University

The pandemic of COVID-19 changed the traditional approaches to the management of gestational complications. Today there is still a lack of information about the impact of COVID-19 on the pregnancy course, in particular, about its role in relation to Rh-conflict during pregnancy.

The paper focused on a rare presentation of Rh-conflict pregnancy and COVID-19. 32 years old G3 P2 pregnant women with Rh-negative had a third pregnancy. The injection of anti-D immunoglobulin after the first abortion was not performed. The second pregnancy finished with a term delivery and the birth of a fetus with hemolytic disease. During the third pregnancy, the woman fell ill with COVID-19 in the 26th week. The bilateral pneumonia was diagnosed.

The treatment included antibiotics, antiviral, antithrombotic, and anti-inflammatory drugs. No signs of fetal hemolytic disease were found via ultrasonography. But the abnormal level of anti-D antibodies – 1:1024 was detected. From the 28th weeks of pregnancy till the delivery the test for anti-D antibodies was constant – 1:4. The variables of utero-placental, fetal (blood flow velocity in a middle cerebral artery), and umbilical hemodynamics were normal during the third trimester. But fetal moderate hepatomegaly and splenomegaly were found at 36 weeks of gestation.

The patient delivered at 38 weeks of gestation a female newborn 3100 g, 52 cm with a 7–8 Apgar score. The laboratory investigation detected a hemoglobin value of 202.6 mg/dL in a child. The blood analysis showed total bilirubin of 44.2 mg/dL, direct bilirubin of 1.0 mg/dL, and a negative result on the direct Coombs test. The baby received phototherapy for 3 days. Total bilirubin was decreased (15.2 mg/dL). The newborn was discharged from a hospital with the mother on the fifth day.

COVID-19 could change the placental permeability and increase the titer of anti-D antibodies. But it did not contribute to fetal and newborn hemolytic disease.

**Keywords:** COVID-19, pregnancy, hemolytic disease of the fetus and newborn, placental barrier.

## COVID-19 імітував гемолітичну хворобу плода: опис випадку

**I. В. Лахно**

Пандемія COVID-19 змінила традиційні підходи до лікування гестаційних ускладнень. На сьогодні ще бракує інформації про вплив COVID-19 на перебіг вагітності, зокрема, про його роль щодо резус-конфлікту під час вагітності. Стаття описує випадок резус-конфліктної вагітності, яка перебігала на фоні COVID-19. Жінка 32 років з негативним резусом мала третю вагітність. Ін'екцію анти-D-імуноглобуліну після першої вагітності, яка закінчилась абортом, її не проводили. Друга вагітність закінчилась терміновими пологами та народженням плода з гемолітичною хворобою. Під час третьої вагітності жінка захворіла на COVID-19 на 26-у тижні. Було діагностовано двобічну пневмонію.

Призначено лікування, що включало антибіотики, противірусні, антитромботичні та протизапальні засоби. Під час ультразвукового дослідження ознак гемолітичної хвороби плода не було виявлено. Але було виявлено аномальний рівень анти-D-антитіл – 1:1024. З 28 тижнів гестації до пологів тест на анти-D-антитіла залишався постійним – 1:4. Параметри матково-плацентарної, плодової (швидкість кровотоку у середній мозковій артерії) та пуповинної гемодинаміки протягом III триместра були у нормі. Але на 36-у тижні гестації виявлено помірну гепато- та спленомегалію у плода.

Жінка народила на 38-у тижні вагітності живу доношенню дівчинку масою тіла 3100 г, довжиною 52 см з оцінкою за шкалою Апгар 7–8 балів. Під час лабораторного дослідження гемоглобін у дитини був 202,6 мг/дл. Аналіз крові зафіксував рівень загального білірубіну 44,2 мг/дл, прямого білірубіну – 1,0 мг/дл і негативний результат прямої проби Кумбса. Дитині проводили фототерапію протягом 3 днів. Загальний білірубін був знижений (15,2 мг/дл). На п'яту добу новонароджену разом із матір'ю виписали додому.

COVID-19, можливо, підвищив проникність плаценти, що призвело до зростання титру анти-D-антитіл. Але це не сприяло розвитку гемолітичної хвороби плода та новонародженого.

**Ключові слова:** COVID-19, вагітність, гемолітична хвороба плода і новонародженого, плацентарний бар'єр.

The pandemic of COVID-19 changed the conventional approaches to the management of gestational complications. The increased level of still-birth, preterm delivery, and fetal growth restriction was detected in pregnant ladies with COVID-19. This infection has a negative effect on maternal and fetal organisms [1, 2]. Since the placenta protects the fetus from maternal infection, the status of the

placental barrier in COVID-19 is of great interest. The inflammatory process in placental villi could induce chronic placental insufficiency and fetal deterioration [3, 4]. There are some studies that showed abnormal uteroplacental hemodynamics due to hypercoagulative status and thrombosis of the placental vessels [5]. The elevated D-dimer level is a typical laboratory marker for COVID-19 during preg-

nancy [6]. The changes in placental structure could be the result of a cytokine storm [7].

Rh-incompatibility is a well-known reason for fetal erythroblastosis [8]. The strategy for the prevention of fetal and neonatal hemolytic disease in Rh-negative mothers was adopted all over the world. But, sometimes, the injection of RhoGAM was not performed in very rare cases. The reasons are a disaster, low social and economic development, maternal refusal, etc. The fetus is at risk of erythroblastosis in subsequent pregnancies. The level of anti-D antibodies in maternal blood and ultrasonic findings are the main components of the management of such a population [9]. The stability of the maternal-fetal interface is an important factor in the pathogenic scenario of fetal hemolytic disease [8]. The increased permeability of the placental barrier could be thought of as a result of viral infections [3]. There is a lack of information on Rh-incompatibility and COVID-19. The transient fetal skin edema in women with COVID-19 was found in several cases [10]. There are only two reports of non-immune hydrops fetalis in women with COVID-19 [11]. Such ultrasonic findings could mimic fetal erythroblastosis.

The issues of health protection are very sound nowadays. The invasion of Russian troops severely complicated the humanitarian situation in Kharkiv. But Kharkiv municipal perinatal center received humanitarian aid from "Doctors without borders". This noble action supported our obstetric service by following the guidelines in disaster settings [12, 13]. Therefore, not only the COVID-19 pandemic but armed conflict complicated the activity of the Ukrainian health care system.

The paper is focused on a rare presentation of Rh-conflict pregnancy and COVID-19.

*Case presentation.* 32 years old G3 P2 pregnant Rh-negative lady had a third pregnancy. The injection of anti-D immunoglobulin after the first abortion was not performed. The second pregnancy was completed by the delivery of the baby with the hemolytic disease at term. All routine I trimester laboratory tests during this pregnancy were normal. The test for anti-D antibodies was negative. The biochemical and ultrasonic screenings had not revealed any abnormalities.

She was fallen ill with COVID-19 at 26 weeks of gestation. She was sent to the department of feto-maternal medicine. The bilateral pneumonia was diagnosed. The conventional treatment including antibiotics, antiviral, anti-thrombotic, and anti-inflammatory drugs was prescribed. She received per os favipiravir 800 mg per day, azithromycin 500 mg twice per day, oseltamivir 75 mg once per day, ceftriaxone 1 g intravenously once per day, enoxaparin 0.4 subcutaneously per day. The duration of basic course of treatment was 2 weeks. The fetal status was not disturbed according to the Doppler ultrasound. No signs of fetal hemolytic disease were found via ultrasonography. But the abnormal level of anti-D antibodies – 1:1024 was detected. The D-dimer concentration was abnormally high – 10.5 µg/mL FEU<sup>3</sup>.

She's recovered soon at 28 weeks of gestation. But the D-dimer level persisted to stay very high for the whole pregnancy. Therefore, the use of anticoagulants was prolonged. She continued receiving enoxaparin sodium 40 mg per day even after discharge till 38 weeks of gestation. The level of anti-D antibodies was fallen to 1:4. From 28 weeks till the time of pregnancy termination the test for anti-D

antibodies stayed constant – 1:4. The variables of utero-placental, fetal (blood flow velocity in a middle cerebral artery), and umbilical hemodynamics were normal during the third trimester. But fetal moderate hepatomegaly were found at 36 weeks of gestation.

She has delivered at 38 weeks of gestation a female newborn 3100 g, 52 sm with a 7–8 Apgar score. The baby had slight respiratory disorders (transient tachypnea). The pneumonia was ruled out via chest X-ray. The tests for COVID-19 were found negative. The markers of inflammation were negative: white blood cell count was 8000/mm<sup>3</sup>, and C-reactive protein was 0.5 mg/l. The laboratory investigation detected a hemoglobin value of 202.6 mg/dL. The blood analysis showed total bilirubin of 44.2 mg/dL, direct bilirubin of 1.0 mg/dL, and a negative result on the direct Coombs test. The baby received phototherapy for 3 days. Total bilirubin was decreased (15.2 mg/dL). The newborn was sent home with the mother on the fifth day.

The presented case report showed an abnormally high level of anti-D antibodies in a pregnant woman with Rh-conflict and COVID-19. Probably, specific acute inflammation induced placental villitis or compensatory changes [1]. The disturbed utero-placental hemodynamics is associated with hypercoagulative status in COVID-19 [6]. Since the transplacental transmission of COVID-19 is possible but not evident, the adaptation of the placental barrier must be thought of [4]. The increased permeability of the placental barrier could be directed on the support of trophotropic reactions in the process of fetal nutrition. This peculiarity should be included in the clinical protocols of such a population. But the speculation requires further investigations.

The changes in immunity and increased intra-abdominal pressure during gestation increase the susceptibility to infections and speed up the progression to respiratory failure in pregnant women, especially if the cardiovascular system is affected [14–16]. Pregnant women with COVID-19 thus have a risk of developing severe pneumonia. Reportedly, risk profiling, including radiological images and PCR, at the time of admission, may improve the chances of risk identification as well as the prognosis in such patients [6, 17, 18]. But in this case, the recovery was speedy.

The hypercoagulative status is typical for pregnant patients with COVID-19 [19–21]. The increased D-dimer level is known as a significant marker for COVID-19. The elevated concentration of D-dimer is an indication for the onset of treatment in the presence of typical clinical symptoms even without polymerase chain reaction (PCR) verification of COVID-19. PCR positivity in COVID-19 could be inferred in a specific group of pregnant women based on the symptoms, e.g., headache, fever, and D-dimer, with a relatively high sensitivity but low specificity. [22–24]. Our patient received anticoagulation for several months.

Fetal hydrops and even fetal demise are possible in Rh-conflict women with anti-D antibodies level 1:16 or higher [8]. Thus, a considerable increase in this variable could stimulate preterm pregnancy termination at 26 weeks of gestation. But the normal value of blood flow velocity in a middle cerebral artery supported the conservative management. Therefore, the use of Doppler ultrasound contributed to pregnancy prolongation and achievement of fetal maturity.

The main issue in the conflict area is the feeling of being in an unsafe environment and unprotected [12]. Our pregnant woman demonstrated courage and a brave spirit. She stayed home and delivered baby in the local perinatal center. She was aware of all risks of delivery under bombardment.

Military situation in Kharkiv is critically involved in the management of pregnant women. Following the evidence-based clinical protocols was the main rule that contributed to beneficial maternal and perinatal outcomes [12, 13]. The use of modern perinatal technologies captured the significant professional level of the staff. The absence of obstetric aggression was based on the current approaches to labor induction [25]. Active management was a measure for the prevention of prolonged stay in the clinic. It was not possible to collect patients in the department of feto-maternal medicine. The delayed stay in the clinic was associated with an increased risk of damage. Thus, early discharge was a measure for the reduction of traumatic injuries.

## CONCLUSION

COVID-19 could change the placental permeability and increase the titer of anti-D antibodies. But it did not contribute to fetal and newborn hemolytic disease.

*Acknowledgements:* none.

*Competing interests:* no conflict of interest was declared by the author.

*Funding:* the author declared that this study has received no financial support.

*Patient consent:* the patient gave her informed consent to participate in the study. The patient provided written informed consent for the publication.

*Ethical approval:* the study was approved by the Research Council and Ethical Committee of Kharkiv National Medical University, No 19.0522 p., and performed in accordance with the principles of the Declaration of Helsinki.

## Information about the author

**Lakhno Igor V.** – MD, PhD, DSc, Professor, Head of the Department of Obstetrics and Gynecology No 3, Kharkiv National Medical University; tel.: (095) 534-72-08, fax: (057) 711-80-25. E-mail: igorlakhno71@gmail.com; iv.lakhno@knmu.edu.ua

## Відомості про автора

**Лахно Ігор Вікторович** – д-р мед. наук, проф., в.о. завідувача, кафедра акушерства та гінекології № 3, Харківський національний медичний університет; тел.: (095) 534-72-08, факс: (057) 711-80-25. E-mail: igorlakhno71@gmail.com; iv.lakhno@knmu.edu.ua

## REFERENCES

- Rad HS, Rhi J, Stylianou N, Allenby MC, Bazaz SR, Warkiani ME, et al. The Effects of COVID-19 on the Placenta During Pregnancy. *Front Immunol.* 2021;12:743022. doi: 10.3389/fimmu.2021.743022.
- Uzel K, Lakhno IV. A Mortal Case of Coronavirus Disease in a Pregnant Diabetic Woman. Clinical Case. *Reprod Endocrinol.* 2020;52:33-6. doi: 10.18370/2309-4117.2020.52.33-36.
- Yong HEJ, Chan Sh, Chakraborty A, et al. Significance of the placental barrier in antenatal viral infections *Biochim Biophys Acta Mol Basis Dis.* 2021;1867(12):166244. doi: 10.1016/j.bbadiis.2021.166244.
- Komine-Aizawa S, Takada K, Hayakawa S. Placental barrier against COVID-19. *Placenta.* 2020;99:45-9. doi: 10.1016/j.placenta.2020.07.022.
- Arora D, Rajmohan KS, Singh S, Nair V, Barui S, Dey M, et al. Correlation between placental histopathology and perinatal outcome in COVID-19. *Tzu Chi Med J.* 2022;34(3):329-36. doi: 10.4103/tcmj.tcmj\_233\_21.
- Uzel K, Lakhno I. PCR positivity and D-dimer levels in pregnant women with COVID-19. *Clin. Exp. Obstet. Gynecol.* 2020;47(5):638-44. doi: 10.31083/j.cieg.2020.05.2229.
- Murphy CA, O'Reilly DP, Edebiri O, Weiss L, Cullinan S, El-Khuffash A, ET AL. Haematological parameters and coagulation in umbilical cord blood following COVID-19 infection in pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2021;266:99-105. doi: 10.1016/j.ejogrb.2021.09.019.
- Nassar GN, Wehbe C. Erythroblastosis Fetalis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513292/>.
- ACOG Practice Bulletin No. 192. Management of Alloimmunization During Pregnancy. *Obst Gynecol.* 2018;131(3):82-90. doi: 10.1097/AOG.0000000000002528.
- Garcia-Manau P, Garcia-Ruiz I, Rodo C, Sulleiro E, Maiz N, Catalan M, et al. Fetal Transient Skin Edema in Two Pregnant Women With Coronavirus Disease 2019 (COVID-19). *Obstet Gynecol.* 2020;136(5):1016-20. doi: 10.1097/AOG.00000000000004059.
- Popescu DE, Cioca A, Muresan C, Navalcan D, Gui A, Pop O, et al. A Case of COVID-19 Pregnancy Complicated with Hydrops Fetalis and Intrauterine Death. *Medicina (Kaunas).* 2021;57(7):667. doi: 10.3390/medicina57070667.
- Joseph NT, Curtis BH, Goodman A. Disaster settings: Care of pregnant patients [Internet]. UpToDate. 2022. Available from: <https://www.uptodate.com/contents/disaster-settings-care-of-pregnant-patients>.
- Lakhno I. The Insight into Obstetric Care near the Front Line in Kharkiv. *Acta Med Lit.* 2022;29(2):236-44. doi: 10.15388/amed.2022.29.2.10.
- Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. *J Reprod Immunol.* 2020;139:103122. doi: 10.1016/j.jri.2020.103122.
- Dashraath P, Wong JLJ, Lim MKK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol.* 2020;222(6):521-31. doi: 10.1016/j.ajog.2020.03.021.
- Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol.* 2020;222(5):415-26. doi: 10.1016/j.ajog.2020.02.017.
- AlZaghali LA, AlZaghali N, Alomari SO, Obeidat N, Obeidat B, Hayajneh WA. Multidisciplinary team management and cesarean delivery for a Jordanian woman infected with SARS-CoV-2: A case report. *Case Rep Womens Health.* 2020;27:e00212. doi: 10.1016/j.crwh.2020.e00212.
- Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. *Physiol Rev.* 2021;101(1):303-18. doi: 10.1152/physrev.00024.2020.
- Gulic T, Blagojevic Zagorac G. COVID-19 and pregnancy: are they friends or enemies? *Horm Mol Biol Clin Investig.* 2021;42(1):57-62. doi: 10.1515/hmbci-2020-0054.
- Salma U. Relationship of COVID-19 with pregnancy. *Taiwan J Obstet Gynecol.* 2021;60(3):405-11. doi: 10.1016/j.tjog.2021.03.005.
- Al Riyami N, Sheik S. COVID-19 and Pregnancy: A narrative review of maternal and perinatal outcomes. *Sultan Qaboos Univ Med J.* 2022;22(2):167-78. doi: 10.18295/squmj.8.2021.120.
- Kucirka LM, Norton A, Sheffield JS. Severity of COVID-19 in pregnancy: A review of current evidence. *Am J Reprod Immunol.* 2020;84(5):e13332. doi: 10.1111/aji.13332.
- Misra SS, Ahirwar AK, Sakarde A, Kaim K, Ahirwar P, Jahid M, et al. COVID-19 infection in pregnancy: a review of existing knowledge. *Horm Mol Biol Clin Investig.* 2022;43(3):373-8. doi: 10.1515/hmbci-2021-0081.
- Newman C, Henderson C, Laraque-Arena D. COVID-19 and Pregnancy: A public health, evidence-based approach. *J Natl Med Assoc.* 2022;114(1):42-6. doi: 10.1016/j.jnma.2021.12.004.
- Rydahl E, Eriksen L, Juul M. Effects of induction of labor prior to post-term in low-risk pregnancies: a systematic review. *JBI Database System Rev Implement Rep.* 2019;17(2):170-208. doi: 10.11124/JBIS-RIR-2017-003587.

Стаття надійшла до редакції 07.02.2023. – Дата першого рішення 15.02.2023. – Стаття подана до друку 22.03.2023