COVID-19 in pregnancy: underestimated risk

Martina Montagnana[1], Brandon M. Henry[2,3], Giuseppe Lippi[1]
[1]Section of Clinical Biochemistry and School of Medicine, University of Verona, Verona, Italy
[2]Clinical Laboratory, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[3]Disease Intervention & Prevention and Population Health Programs, Texas Biomedical Research Institute, San Antonio, Texas, USA

ABSTRACT

The almost relentless worldwide diffusion of severe acute respiratory syndrome coronavirus (SARS-CoV-2) is deeply engaging the minds of many scientists, clinicians and laboratory professionals, who struggle to identify the possible short- and long-term consequences of coronavirus disease 2019 (COVID-19) in the general population, as well as in specific cohorts of individuals, who may display peculiar features of infection. Pregnant women represent one of these categories, since the biological implications of SARS-CoV-2 infection extend far beyond those caused to the mother, involving also the fetus. Several lines of evidence now attest that although mother-to-child SARS-CoV-2 transmission is relatively rare (<2% of all pregnancies), the consequences on maternal-fetal-neonatal interface of COVID-19 can be very serious. To this end, some important questions raise, such as "is COVID-19 a risk factor for complications in pregnancy?", "which laboratory tests are more predictable of unfavorable pregnancy outcomes?", "how efficacious is COVID-19 vaccination in pregnancy?" and, last but not least, "what evidence supports laboratory monitoring of COVID-19 vaccination immunogenicity in pregnancy?". In this opinion paper, we will attempt to provide an overview of the current biological, clinical and laboratory evidence of SARS-CoV-2 infection in pregnancy, trying also to provide reliable answers to the aforementioned questions.

Keywords: *SARS-CoV-2; Pregnancy; Laboratory Medicine*

THE FOUR QUESTIONS

Is covid-19 a risk factor for complications in pregnancy?

Although mother-to-child transmission (*in utero*, *intrapartum*, or early postnatal) of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is relatively rare, occurring in less than 2% of all pregnancies [1.8%; 95% confidence interval (95%IC) 1.2-2.5] according to data from a recent meta-analysis including 206 cohort and 266 case studies, and totaling 28 952 mothers and 18 237 babies (1), it is clear that the consequences of coronavirus disease 2019 (COVID-19) on the maternal-fetal-neonatal interface even in the absence of mother-to-child transmission can be very serious, as summarized in Figure 1. Since COVID-19 is now widely universally recognized as an infective vascular disorder, it is not surprising that some specific vascular complications may be triggered by SARS-CoV-2 infection. In the large INTERCOVID prospective longitudinal study (2), including 2184 pregnant women (33.2% of whom with a diagnosis of SARS-CoV-2 infection), the authors found that the risk of preeclampsia was nearly 2-fold higher in pregnant women with a diagnosis of COVID-19 compared to those without (risk ratio, 1.77; 95%CI, 1.25-2.52), and such risk was slightly higher in nulliparous women (risk ratio, 1.89; 95%CI, 1.17-3.05). Importantly, the risk of preeclampsia was similar between women with asymptomatic or symptomatic SARS-CoV-2

Corresponding author: Giuseppe Lippi, Section of Clinical Biochemistry University Hospital of Verona, Piazzale L.A. Scuro, 10 37134 Verona – Italy, Email: giuseppe.lippi@univr.it

Received: 19.03.2022 Revised: 22.03.2022 Accepted: 23.03.2022

Published on-line: 10.04.2022 DOI: 10.19186/BC_2022.018

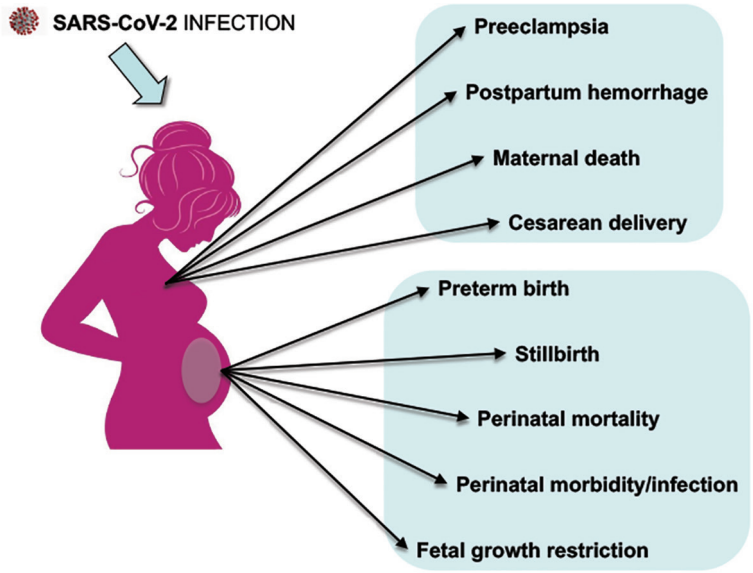

Figure 1
Adverse clinical consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pregnancy.

infection (risk ratio 1.70 *versus* 1.81). In an even broader perspective nationwide US analysis conducted by Regan et al. and including 78 283 pregnancies (3), SARS-CoV-2 infection was associated with a vast array of unfavorable outcomes, including abortion hazard ratio (HR), 2.60; 95%CI, 1.17-5.78), clinician-initiated preterm birth (HR, 2.88; 95%CI, 1.93-4.30), spontaneous preterm birth (HR, 1.79; 95%CI, 1.37-2.34), cesarean delivery (HR, 1.99; 95%CI, 1.71-2.31) as well as fetal growth restriction (HR, 2.04; 95%CI, 1.72-2.43). These results were confirmed by another large multicenter US-based study organized by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (4). This large retrospective cohort investigation, including 14 104 pregnant women (16.7% with SARS-CoV-2 infection), evidenced that COVID-19 was associated with a higher risk of a composite endpoint of maternal death, morbidity due to hypertensive disorders of pregnancy, or postpartum hemorrhage (relative risk, 1.41; 95%CI, 1.23-1.61). Such risk was magnified in women with moderate or severe forms of COVID-19 illness (relative risk, 2.06; 95%CI, 1.73-2.46). A recent meta-analysis summarized the finding of many individual studies which linked SARS-CoV-2 infection to obstetric and perinatal pregnancy outcomes (5). Overall, 17 observational studies totaling 16 576 pregnancies (16.7% with SARS-CoV-2 infection) were included in the final analysis, which confirmed that a diagnosis of COVID-19 was associated with higher risk of preeclampsia [odds ratio (OR), 1.30; 95%CI 1.09-1.54], neonatal intensive care unit (NICU) admission (OR, 2.37; 95%CI, 1.18-4.76), stillbirth (OR, 2.70; 95%CI, 1.38-5.29) and perinatal mortality (OR, 3.23; 95%CI 1.23-8.52).

The main underlying mechanisms of pregnancy complications point to a clear vascular basis, as demonstrated by a study based on placenta and post-mortem examinations of fetuses from COVID-19 women who developed a pregnancy complication (6). Briefly, the main histopathological findings were the presence of trophoblast necrosis due to virus penetration, massive inflammation in villous chamber, chronic histiocytic intervillositis, large intervillous thrombi with massive perivillous fibrin deposition, all events associated with high SARS-CoV-2 expression in trophoblast and amniotic fluid. In another post-mortem study published by Reagan-Steiner et al. (7), the authors found severe diffuse alveolar damage and localized SARS-CoV-2 in neonatal pulmonary tissue, along with viral RNA in neonatal heart, liver vascular endothelium and placenta, thus indicating that in utero SARS-CoV-2 transmission may have actively contributed to neonatal death. The association between COVID-19 and pregnancy complication finds a reasonable biological background in that both angiotensin converting enzyme 2 (ACE2; the natural SARS-CoV-2 receptor at cell surface) and transmembrane serine protease 2 (TMPRSS2), key elements driving virus entrance in the host cells, are significantly expressed in trophoblast cells, thus making this tissue vulnerable to SARS-CoV-2 infection (8). This is consistent with the fact that placentitis is often associated with maternal viremia, as shown by Mithal et al. (9). Interestingly, elevated pro-inflammatory cytokines have been reported in neonatal cord blood, even in the absence of placental infection (10). The long-term impact of non-specific imprinting of neonatal immune system in those born to SARS-CoV-2-exposed mothers remains to be elucidated.

Which laboratory tests are predictable of unfavorable pregnancy outcomes?

A comprehensive meta-analysis of laboratory abnormalities encountered in pregnant women with SARS-CoV-2 infection and their newborns was published by

Zhang et al. (11). In summary, the most evident laboratory findings encompassed increased neutrophils count and IgG (in >50% women and neonates), increased values of C reactive protein (CRP) and reduced hemoglobin levels (in >50% women). Lymphopenia was also relatively frequent in mothers (>30%), whilst increased levels of liver enzymes (alanine aminotransferase and/or aspartate aminotransferase) were also commonplace in neonatal blood (>60%). Thrombocytopenia and increased procalcitonin concentration were also found in 20-30% of neonates. In a separate meta-analysis conducted by Khalil et al. (12), the authors identified additional laboratory abnormalities in pregnant women diagnosed with SARS-CoV-2 infection, including elevated D-dimer values (85%), along with increased concentration of CRP or procalcitonin (54%). In keeping with these findings, Kalafat et al. carried out a multicenter retrospective cohort from 8 different hospitals in 4 distinct countries, totaling 793 SARS-CoV-2 positive pregnancy, 5.5% of whom admitted to the intensive care unit (ICU) and 1.3% who died during hospital stay (13). The model developed for predicting adverse pregnancy outcome, which included various demographical and clinical variables (such as maternal age, body mass index, ethnicity and comorbidities among others), symptoms and laboratory data (i.e., neutrophil to lymphocyte ratio and CRP) displayed a considerable accuracy, with an area under the curve (AUC) as high as 0.85.

How efficacious is COVID-19 vaccination in pregnancy?

The evidence that COVID-19 vaccination is the most effective strategy not only for preventing the unfavorable consequences of SAR-CoV-2 infection (14), but also to limit virus circulation, is now almost unquestionable (15).

The largest study to-date on vaccine efficacy in pregnancy was published by Dagan et al. (16). The authors compared the ratio of SARS-CoV-2 infection, COVID-19-related hospitalization, severe illness and death in 10 861 pregnant women who received the mRNA-based BNT162b2 vaccine *versus* 10 861 unvaccinated matched pregnant women. Overall, vaccine efficacy between 7-56 days after completing the primary vaccination cycle was estimated at 96% (95%CI, 89-100) for all forms of SARS-Cov-2 infection, 97% (95%CI, 91-100) for symptomatic infections, and as high as 89% (95%CI, 43-100) for COVID-19-related hospitalization (no deaths occurred in both groups). In another retrospective cohort study based on a pregnancy registry in Israel including 7 530 pregnant women who received the mRNA-based BNT162b2 vaccine and 7 530 matched unvaccinated controls (17), vaccine efficacy against any type of SARS-CoV-2 infection 28-70 days after completing primary vaccination was 78% (95%CI, 57-89). Similar results were obtained in another smaller study (including 407 pregnant recipients of mRNA-based vaccines and 407 unvaccinated matched women) (18), vaccine efficacy against SARS-CoV-2 infection was 88% (95%CI, 44-97) 14 days after receiving the second vaccine dose. Such remarkable vaccine efficacy is then compounded by very high safety profile of mRNA-based vaccination at any stage of pregnancy, as recently highlighted by Bookstein Peretz et al. (19).

It is also very important to underline that maternal vaccination during pregnancy is also highly effective against the risk of COVID-19-related morbidity and mortality in infants. Thus, vaccines not only protect the mother, but also protect their children. A comprehensive study carried out by Halasa et al. in 20 US pediatric hospitals (20), evidenced that maternal vaccination was effective to reduce COVID-19-related hospitalizations of infants aged <6 months by 61% (95%CI, 31-78). It should be noted, however, that full data on vaccine efficacy following emergence of the high immune escape Omicron variant in pregnant women is not yet widely available for analysis. Nonetheless, based on observations in the overall population, vaccination, especially with booster doses, is likely to continue to provide sufficient protection against hospitalization and severe illness in pregnant women.

Altogether, the available evidence has persuaded the Italian National Institute of Health (Istituto Superiore di Sanità; ISS), to endorse some *ad interim* recommendations on pregnancy vaccination (21), which basically encompass to offer primary mRNA vaccination followed by a booster vaccine dose to all pregnant women in the second and third trimester, at least to those willing to be vaccinated.

What evidence supports laboratory monitoring of COVID-19 vaccination immunogenicity in pregnancy?

A recent meta-analysis aimed at summarizing the kinetics of anti-SARS-CoV-2 antibodies in pregnancy and encompassing 13 observational studies totaling 48 039 pregnant women who received mRNA-based vaccines observed that neutralizing immunoglobulins increased rapidly after the primary vaccination cycle (22), increasing further after receiving the vaccine booster dose and enhancing their transplacental transportation. Nonetheless, evidence is emerging that immunogenicity of COVID-19 vaccines may be slightly lower in pregnancy. In a prospective cohort study including 96 pregnant women and 96 matched non-pregnant controls who all received the mRNA-based BNT162b2 vaccine (23), the pregnant cohort had anti-SARS-CoV-2 IgG antibodies levels 21% lower than the non-pregnant cohort (27±11 *versus* 34±10 U/L; p<0.001).

Importantly, evidence has also emerged that pregnant women receiving mRNA-based vaccines develop anti-SARS-CoV-2 Spike IgG antibodies which undergo transplacental passage, thus being actively transmitted to the fetus, who display values significantly correlated with those found in the mother (24). In a prospective cohort study including 58 pregnant women who received the mRNA-based BNT162b2 vaccine (25), anti-SARS-CoV-2 IgG antibodies levels in maternal sera and fetal cord blood sera were found to be significantly correlated (r= 0.857; p<0.001), with a ratio of maternal-to-umbilical cord values of approximately 1. Importantly, the presence

Table 1
Main characteristics of coronavirus disease 2019 (COVID-19) and vaccination in pregnancy

Feature	Evidence
COVID-19 in pregnancy	Although mother-to-child SARS-CoV-2 transmission is relatively rare, the consequences on the maternal-fetal-neonatal interface of COVID-19 can be serious
COVID-19 vaccination in pregnancy	Highly effective for preventing SARS-CoV-2 infection and related complications
	Displays high safety profile in pregnancy (both for the mother and the fetus)
	Elicits a substantial production of anti-SARS-CoV-2 antibodies in pregnant women
	Kinetics of anti-SARS-CoV-2 antibodies comparable to that of non-pregnant controls
	Serum levels of anti-SARS-CoV-2 antibodies may be slightly lower than in non-pregnant women
	Anti-SARS-CoV-2 antibodies undergo transplacental passage, with maternal-to-umbilical cord values highly correlated (ratio ~1)
	Anti-SARS-CoV-2 antibodies (both IgA and IgG) are also present in human milk during lactation

of anti-SARS-CoV-2 antibodies in fetal serum is most likely attributable to maternal delivery, since SARS-CoV-2 mRNA cannot be detected in the breast milk of COVID-19 mRNA vaccine recipients (26). Important evidence, which emerged from several studies, has also confirmed that mRNA COVID-19 vaccines are highly immunogenic in pregnancy, and vaccine-elicited antibodies not only could be transported to the infant through the cord blood, but are also present in breast milk (27). In the study by Young et al. (28), the presence and persistence of anti-SARS-CoV-2 neutralizing antibodies in human milk was thoroughly investigated. The results showed that both anti-SARS-CoV-2 neutralizing IgA and IgG can be elicited at sustained levels in milk by administration of mRNA-based vaccines, and that IgA antibodies persisted almost unvaried in milk for up to 72 days after receiving the last vaccine dose. Interestingly, when mRNA-based and adenoviral COVID-19 vaccines were compared, the former category was found to elicit a considerably higher level of anti-SARS-CoV-2 antibodies in human milk (29).

As the kinetics of anti-SARS-CoV-2 serum antibodies levels is concerning, a study found that each week passed since completing primary COVID-19 vaccination, maternal and neonatal antibodies decreased by ~11% (95%CI, 4-17) and 12% (95%CI, 4-19), respectively (30). These results were confirmed in another study (31), which found a trend towards delayed kinetics of anti-SARS-CoV-2 Fc receptor (FcR) binding and antibody effector functions after receiving mRNA-based vaccination in pregnant and lactating women compared with nonpregnant controls.

Overall, COVID-19 vaccination in pregnancy is hence associated with development of efficient SARS-CoV-2 neutralizing antibodies throughout pregnancy up to delivery, though some heterogeneous variations across pregnant women are consistent with the hypothesis of establishing a periodical serological monitoring.

CONCLUSIONS

Several lines of evidence now attest that SARS-CoV-2 infection may cause severe consequences in pregnancy, both to the mother and the fetus, thus paving the way to recommend widespread COVID-19 vaccination, since current vaccines are effective (Table 1), and have a high safety profile in pregnancy, leaving gestation, childbirth and perinatal morbidity almost unvaried (32). This is consistent with the fact that severe forms of COVID-19 in pregnancy almost exclusively develop in unvaccinated women, or in those with lower vaccine immunogenicity (33). Although the kinetics of anti-SARS-CoV-2 antibodies in pregnancy seems globally comparable to that observed in non-pregnant controls, their serum levels may be slightly lower. Heterogeneous immunogenicity, which is then correlated with transplacental passage and human milk presence has also been observed in pregnant and lactating women, which would suggest that anti-SARS-CoV-2 antibodies monitoring may be advisable throughout pregnancy and lactation, to timely identify women at higher risk of SARS-CoV-2 infection and COVID-19 complications, who may potentially benefit more by receiving adjunctive vaccine boosters to protect themselves and their children (34,35).

REFERENCES

1. Allotey J, Chatterjee S, Kew T, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. BMJ 2022;376:e067696.
2. Papageorghiou AT, Deruelle P, Gunier RB, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. Am J Obstet Gynecol 2021;225:289.e1-289.e17.
3. Regan AK, Arah OA, Fell DB, Sullivan SG. SARS-CoV-2

Infection During Pregnancy and Associated Perinatal Health Outcomes: A National US Cohort Study. J Infect Dis 2022;225:759-67.
4. Metz TD, Clifton RG, Hughes BL, et al. Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications. JAMA 2022;327:748-59.
5. Pérez-López FR, Savirón-Cornudella R, Chedraui P, et al. Obstetric and perinatal outcomes of pregnancies with COVID 19: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2022 doi: 10.1080/14767058.2022.2051008. Epub ahead of print.
6. Bouachba A, Allias F, Nadaud B, et al. Placental lesions and SARS-Cov-2 infection: Diffuse placenta damage associated to poor fetal outcome. Placenta 2021;112:97-104.
7. Reagan-Steiner S, Bhatnagar J, Martines RB, et al. Detection of SARS-CoV-2 in Neonatal Autopsy Tissues and Placenta. Emerg Infect Dis 2022;28:510-7.
8. Zhou J, Choi S, Liu H, et al. Is SARS-CoV-2 Infection a risk factor for early pregnancy loss? ACE2 and TMPRSS2 co-expression and persistent replicative infection in primitive trophoblast. J Infect Dis 2021;224:S660-9.
9. Mithal LB, Otero S, Simons LM, et al. Low-level SARS-CoV-2 viremia coincident with COVID placentitis and stillbirth. Placenta 2022;121:79-81.
10. Gee S, Chandiramani M, Seow J, et al. The legacy of maternal SARS-CoV-2 infection on the immunology of the neonate. Nat Immunol 2021;22:1490-502.
11. Zhang C, Chu H, Pei YV, Zhang J. Laboratory effects of COVID-19 infection in pregnant women and their newborns: a systematic review and meta-analysis. Front Glob Womens Health 2021;2:647072.
12. Khalil A, Kalafat E, Benlioglu C, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020 Aug;25:100446.
13. Kalafat E, Prasad S, Birol P, et al. An internally validated prediction model for critical COVID-19 infection and intensive care unit admission in symptomatic pregnant women. Am J Obstet Gynecol 2022;226:403.e1-403.e13.
14. Mattiuzzi C, Lippi G. Primary COVID-19 vaccine cycle and booster doses efficacy: analysis of Italian nationwide vaccination campaign. Eur J Public Health. 2022 doi: 10.1093/eurpub/ckab220. Epub ahead of print.
15. Mattiuzzi C, Lippi G. COVID-19 vaccines efficacy in preventing or limiting SARS-CoV-2 infections. J Infect. 2022 doi: 10.1016/j.jinf.2022.01.033. Epub ahead of print.
16. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med 2021;27:1693-5.
17. Goldshtein I, Nevo D, Steinberg DM, et al. Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection in pregnant women. JAMA 2021;326:728-35.
18. Butt AA, Chemaitelly H, Al Khal A et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest 2021;131:e153662.
19. Bookstein Peretz S, Regev N, Novick L, et al. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. Ultrasound Obstet Gynecol 2021;58:450-6.
20. Halasa NB, Olson SM, Staat MA, et al. Effectiveness of maternal vaccination with mRNA COVID-19 vaccine during pregnancy against COVID-19- associated hospitalization in infants aged <6 months - 17 States, July 2021-January 2022. Morb Mortal Wkly Rep 2022;71:264-70.
21. Istituto Superiore di Sanità. COVID-19 vaccination in pregnancy and breastfeeding. Available at: https://www.epicentro.iss.it/en/vaccines/covid-19-pregnancy-breastfeeding. Last accessed: March 2022.
22. Pratama NR, Wafa IA, Budi DS, et al. mRNA Covid-19 vaccines in pregnancy: A systematic review. PLoS One 2022;17:e0261350.
23. Bookstein Peretz S, Regev N, et al. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. Ultrasound Obstet Gynecol 2021;58:450-6.
24. Prabhu M, Murphy EA, Sukhu AC, et al. Antibody response to coronavirus disease 2019 (COVID-19) messenger RNA vaccination in pregnant women and transplacental passage into cord blood. Obstet Gynecol 2021;138:278-80.
25. Ben-Mayor Bashi T, Amikam U, Ashwal E, et al. The association of maternal SARS-CoV-2 vaccination-to-delivery interval and the levels of maternal and cord blood antibodies. Int J Gynaecol Obstet 2022;156:436-43.
26. Golan Y, Prahl M, Cassidy A, et al. Evaluation of messenger RNA from COVID-19 BTN162b2 and mRNA-1273 vaccines in human milk. JAMA Pediatr 2021;175:1069-71.
27. Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. JAMA 2021;325:2370-80.
28. Young BE, Seppo AE, Diaz N, et al. Association of human milk antibody induction, persistence, and neutralizing capacity with SARS-CoV-2 infection versus mRNA vaccination. JAMA Pediatr 2022;176:159-68.
29. Juncker HG, Mulleners SJ, Coenen ERM, et al. Comparing human milk antibody response after 4 different vaccines for COVID-19. JAMA Pediatr. 2022 doi: 10.1001/jamapediatrics.2022.0084. Epub ahead of print.
30. Kugelman N, Nahshon C, Shaked-Mishan P, et al. Maternal and neonatal SARS-CoV-2 immunoglobulin G antibody levels at delivery after receipt of the BNT162b2 messenger RNA COVID-19 vaccine during the second trimester of pregnancy. JAMA Pediatr 2022;176:290-5.
31. Atyeo C, DeRiso EA, Davis C, et al. COVID-19 mRNA vaccines drive differential antibody Fc-functional profiles in pregnant, lactating, and nonpregnant women. Sci Transl Med 2021;13:eabi8631.
32. Leik NKO, Ahmedy F, Guad RM, et al. Covid-19 vaccine and its consequences in pregnancy: Brief review. Ann Med Surg (Lond) 2021;72:103103.
33. Engjom H, van den Akker T, Aabakke A, et al. Severe COVID-19 in pregnancy is almost exclusively limited to unvaccinated women - time for policies to change. Lancet Reg Health Eur 2022;13:100313.
34. Lippi G, Brandon MH, Plebani M. Optimizing effectiveness of COVID-19 vaccination: will laboratory stewardship play a role? Clin Chem Lab Med 2021;59:1885-8.
35. Lippi G, Mattiuzzi C. Il contributo della Medicina di Laboratorio nella campagna vaccinale anti COVID-19. Biochim Clin 2022;46:6-8.