

MINI REVIEW

Action is needed to tackle the clinical, psychological and socioeconomic impact of perinatal COVID-19

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Funding information

This study did not receive any specific funding.

Abstract

The COVID-19 pandemic has turned perinatal healthcare into a worldwide public health challenge. Although initial data did not demonstrate pregnancy as a more susceptible period to adverse outcomes of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, an increasing number of reports now certify maternal illness as a high-risk condition for the development of maternal–fetal complications. Despite the rarity of SARS-CoV-2 vertical transmission, severe maternal illness might induce adverse perinatal and neonatal outcomes. Additionally, perinatal COVID-19 data may raise concerns about long-term harmful consequences to the offspring in the framework of non-communicable diseases. The World Health Organisation, as well as scientific literature, consider the protection of the maternal–fetal dyad against COVID-19 as a critical issue and, therefore, strongly promote and encourage the vaccination of pregnant and lactating women. Furthermore, the pandemic has triggered an unprecedented recession, leading to historic levels of unemployment and deprivation, while health, societal, economic and gender inequities particularly affecting low-income and middle-income countries, have increased. This mini-review provides an updated brief report on historical, clinical, psychological and socioeconomic aspects of the COVID-19 pandemic based on 10 lectures presented at the 9th Maria-Delivoria-Papadopoulos Perinatal Symposium, held virtually on 19 March 2022.

KEYWORDS

COVID-19, perinatal period, placenta, pregnancy, socioeconomic aspects

1 | THE COVID-19 PANDEMIC AND THE PLAGUE OF ATHENS

Over time, pandemics seem to exhibit important similarities in their origin, evolution and outcomes. In this respect, comparable features can be documented between two pandemics 25 centuries apart: the

current COVID-19 pandemic and the so-called Plague of Athens, a serious contagious disease, not necessarily bubonic plague, described by the ancient Athenian historian Thucydides. Both pandemics are characterised by the rivalry of superpowers (USA/China, Athens/Sparta in antiquity) and their alike political systems, conspiracy theories for biological warfare, population congestion, transport and spreading

Abbreviations: COVID-19, Corona Virus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Corona Virus-2; ICU, Intensive Care Unit; ACE2, Angiotensin Converting Enzyme-2; TMPRSS2, Transmembrane Serine Protease 2; WHO, World Health Organisation; Anti-S Ig, Anti-Spike Immunoglobulin; DOHaD, Developmental Origins of Health and Disease; NCD, Non-Communicable Diseases; UNICEF, United Nations International Children's Emergency Fund.

An updated report of the 9th Maria Delivoria-Papadopoulos Perinatal Symposium, 19 March 2022

of the diseases by aircrafts or ships. Also, by preceded and concurrent adverse events (global economic crisis/famine and overloaded sewage systems), mitigations, relapses and waves of the pandemics, attacks of any age, sex, nationality or social group. Furthermore, by the huge number of deaths, several common symptoms, astonishing similarities concerning mental and psychosocial consequences and adverse impact on the healthcare providers. Thus, the considerable number of comparable characteristics between COVID-19 and the Plague of Athens confirms that past pandemics could serve to draw lessons for the present and the future.¹

2 | SUCCESSES AND CHALLENGES DURING THE GREEK PANDEMIC

By April 2020, the infection rate in Greece was 0.12%, one of the lowest in Europe, while the fatality ratio was 1.12%,² possibly due to the implementation of multiple non-pharmaceutical interventions and quick enforcement of a strict lockdown.

Over the next couple of years, an increase in cases was observed as new pandemic waves ensued, mainly due to the predominance of new SARS-CoV-2 variants. Twice a week, rapid antigenic testing and obligatory result reporting in a specially designed platform were implemented since 2021 for students and unvaccinated subjects working in public and private sectors. Due to extensive self-testing and contact tracing, infected Greek children were timely diagnosed allowing schools to remain open during the period 2021–2022.

Achieving high COVID-19 vaccination coverage was the main challenge for the state. By March 2021, 72.0% of the general population and 80.8% of adults were vaccinated with 2 doses, and 72.5% of vaccinated people had received their booster dose.³ Before the Omicron variant prevailed, the number of cases, hospitalisation and death rates in each regional unit were inversely correlated with local vaccination coverage.³ Adolescent vaccination rates followed similar patterns and decreased incidence rate of the COVID-19 infections in regions with high-vaccination coverage was documented. Even in the era of Omicron and Omicron sub-variant predominance, vaccination effectively prevents severe disease and provides significant protection against intensive care unit (ICU) admission, mechanical ventilation and death.

3 | IMPACT ON PREGNANCY AND THE PLACENTA

A continuously updated living systematic review on COVID-19, with the last update in May, 2022 revealed pregnancy as an important risk factor for severe disease, hospitalisation and ICU admission, resulting in a three-fold increase in the risk of preterm birth.⁴ These findings may be related to adaptive changes that occur during pregnancy, such as the reduction in the residual respiratory capacity, the decrease in viral immune responses and the increased risk for thromboembolic events. Nevertheless, a recent study

Key Notes

- COVID-19 in pregnancy is a high-risk condition for the development of maternal–fetal complications.
- Perinatal COVID-19 may raise concerns about long-term harmful consequences to the offspring in the framework of non-communicable diseases, urging for vaccination in pregnancy and lactation.
- The pandemic has triggered an unprecedented recession, leading to unemployment and health, societal, economic and gender inequities, particularly affecting deprived population groups and low-middle income countries.

reported slightly lower preterm birth rates in Denmark during the first year of the COVID-19 pandemic compared with the previous 4 years.⁵ In addition to high body mass index, advanced maternal age and non-white ethnic origin, evidence suggests that pre-existing comorbidities and pregnancy-specific conditions such as preeclampsia and gestational diabetes are risk factors for severe disease.⁴ At the same time, COVID-19 has increased the incidence of preeclampsia and hypertensive disorders of pregnancy, stillbirths, perinatal mortality and Caesarean deliveries, which should only be performed for standard obstetric indications.⁶

During the early days of the pandemic, there was no documented evidence for vertical COVID-19 transmission in women in late pregnancy. According to more recent data, the intrauterine transmission of SARS-CoV-2 is feasible, but appears to be very rare, possibly due to the low levels of viremia and the decreased co-expression of angiotensin-converting enzyme-2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), necessary for viral entry into placental cells. Suggested mechanisms of vertical transmission include direct infection of syncytiotrophoblasts through the syncytial layers, passage through the maternal circulation to extravillous trophoblasts, passage through maternal immune cells and ascending infection via the maternal vaginal tract.⁷

Meta-analyses on the impact of maternal infection on placental histology, documented conflicting results. Lack of typical COVID-19-specific placental changes, such as previously reported inflammatory and microvascular lesions⁸ versus increased prevalence of perivillous fibrin deposition.⁹ Nevertheless, despite placentas being tested positive for SARS-CoV-2, there are very few newborns that manifest in utero-induced disease. Relatively, the most important prognostic factor seems to be maternal–fetal hypoxia in the context of pneumonia.⁷

4 | THE PANDEMIC'S IMPACT ON NEONATES AND BREASTFEEDING

Overall perinatal transmission of SARS-CoV-2 infection from mother to infant appears to be low. Postnatal transmission accounts for the

majority of neonatal infections, likely representing exposure to the infected mother, other caregivers and or the neonatal environment. High rates of positive tests have been recorded in neonates born to mothers with the first positive test within 1 week of delivery and symptomatic mothers. Importantly, the rate of positivity in cases of rooming-in and the risk of transmission via breast milk is estimated to be very low.¹⁰

Adverse neonatal outcomes are mostly associated with worsening maternal COVID-19 illness and in utero hypoxia, which often prompt preterm delivery and delivery via the Caesarean section.¹⁰

Health outcomes of neonates testing positive for SARS-CoV-2 are largely favourable. Infants with the perinatal transmission have no or mild signs of disease,¹⁰ possibly due to some unique biologic and immune characteristics of neonates. These include altered systemic inflammatory response and decreased production of pro-inflammatory mediators. Respiratory symptoms are common, often associated with prematurity, as well as fever, gastrointestinal, cardiovascular and neurological features.¹¹ Clinical symptoms, such as gastrointestinal manifestations and absent sucking reflex, in association with elevated COVID-19 inflammatory/ischemia markers and mild vascular and or inflammatory placental lesions, have also been demonstrated in full-term SARS-CoV-2 negative neonates born to positive mothers with uncomplicated pregnancies. These findings imply a potential impact of peripartum SARS-CoV-2 exposure even on non-infected neonates, which requires further investigation.¹² Neonatal multisystem inflammatory syndrome (MIS-N), which is thought to be a neonatal hyperimmune response to maternal antibodies against the virus, has rarely been reported.

During the COVID-19 pandemic, several international recommendations and guidelines regarding the management of neonates at risk have evolved. To date, no cases of transmission of infectious viral particles to infants through breast milk have been reported. Early breastfeeding provides vital protection during viral infections, due to its high biological value, the content of immunological factors and the specific role of lactoferrin. No differences were prospectively documented in early breast milk lactoferrin between positive mothers and controls, while early human milk of infected mothers displayed IgA and IgG SARS-CoV-2 specific reactivity.¹³ Most importantly, breast milk IgA induced by SARS-CoV-2 infection is comprised of mainly secretory antibody that is neutralising and highly durable over time.¹⁴ These data provide strong evidence for a protective role of breastfeeding.

If mother–infant health status allows it, the World Health Organisation (WHO) recommends rooming-in and breastfeeding or administration of expressed breast milk, provided that strict preventive measures are followed¹⁵. The benefits of bonding through breastfeeding greatly outweigh the low-potential risk of COVID-19 transmission to neonates. In parallel, breastfeeding counselling should focus on further reducing the very low risk of respiratory viral transmission during mother–infant contact.

5 | VACCINATION DURING PREGNANCY AND LACTATION

Even though pregnant women were initially excluded from vaccine trials, several studies have consistently demonstrated that vaccination is effective, safe and immunogenic, generating important benefits for both the mother and newborn. Maternal neutralising antibodies are transmitted through the placenta and breast milk. Therefore, vaccination during the second and third trimesters of pregnancy, as well as during lactation, is currently a priority, recommended by WHO and principal experts' societies.¹⁶

Recent systematic reviews and meta-analyses provided evidence of 89.5% effectiveness after the second dose of mRNA vaccination of pregnant women, lack of increased risk of adverse pregnancy outcomes¹⁷ and high rates of positivity for breast milk antibodies following COVID-19 immunizations, especially after the second dose, depending on vaccine type.¹⁸

However, COVID-19 vaccination prevalence in pregnant women is globally low. Initially, the vaccination campaign occurred in a climate of disorientation and uncertainty, with many healthcare professionals discouraging vaccination due to a lack of knowledge regarding efficacy and safety, leading to maternal refusal or postponement out of fear of causing fetal harm and modification of the breast milk properties.¹⁶ In a recent systematic review and meta-analysis the overall proportion of pregnant women vaccinated against COVID-19 were 27.5%.¹⁹ Predictors of COVID-19 vaccination uptake were older age, ethnicity, race, trust in COVID-19 vaccines and fear of COVID-19 during pregnancy.¹⁹

Recent data showed that BNT161b2 vaccination in late pregnancy or lactation enhances immunity through transplacental transfer of anti-spike immunoglobulin (anti-S Ig), while SARS-CoV-2 infection induces mucosal immunity through breast milk Ig production. The authors suggest that next-generation vaccines boosting mucosal immunity could provide additional protection to the mother–infant dyad.²⁰

6 | METABOLOMICS AND MICROBIOMICS

The SARS-CoV-2 infection has been associated with gut microbiota changes and immune-mediated inflammation, marked by the prevalence of pro-inflammatory bacterial species and the reduction of anti-inflammatory species. Poor prognosis is documented in patients with underlying co-morbidities who have increased gut permeability and reduced gut microbiome diversity. Therefore, the gut-lung cross-talk has been suggested as an important player in excessive immune reactions during both, the infectious phase of the disease and the post-COVID-19 infection recovery period.²¹

Alterations of the host metabolic homeostasis strongly influence immune responses to SARS-CoV-2, resulting in a wide range of outcomes, from asymptomatic infection to life-threatening acute

respiratory distress syndrome. Remarkable changes in the lipid and amino acid metabolism depict the molecular phenotype of subjects infected by SARS-CoV-2.²² Furthermore, distinguishing functional characteristics in COVID-19 respiratory tract microbiomes have been identified, including decreased potential for lipid metabolism and increased potential for carbohydrate metabolism pathways. Several studies are currently investigating the role of probiotics, prebiotics and diet in preventing and reducing susceptibility to SARS-CoV-2 infection.²¹

7 | COVID-19 AND DOHAD ACROSS THE LIFE COURSE

The long-term impact of perinatal COVID-19 is unknown. COVID-19 pandemic may hypothetically increase the risk of non-communicable diseases (NCDs), given its documented association with various perinatal risk factors for later disease in the offspring, such as preterm birth, increased rates of Caesarean section and decreased rates of breastfeeding.²³ In addition, the pandemic has caused widespread school closures and lockdowns leading to unhealthy dietary changes and sedentary living among adolescents and young adults, who are tomorrow's parents.²⁵ According to the mismatch hypothesis, a developmental "mismatch" between a sub-optimal preconceptional-perinatal and an obesogenic childhood environment is related to a particular predisposition to obesity and corresponding comorbidities in childhood.²⁴

The pandemic also impacted mental health and well-being due to disruption of normal life and attenuated depression, anxiety and stress among pregnant women.²⁵ Stress in pregnancy most probably affects cognitive function in the child.²⁶

Strong scientific evidence suggests that maternal/child health and wellbeing significantly affect trans-generational population health, adult prosperity and societal resilience. The effect of the pandemic on long-lasting industries offers opportunities to implement new policies and ways of working. These should be predicated on an economic framework that assigns measurable value to actions that improve the health and wellbeing of women and children.

8 | IMPACT ON THE WELL-BEING OF FAMILIES

The impact of the COVID-19 pandemic on the well-being of women and girls was harmful considering the aspects of economy, health, security and social protection. The decrease in employment between 2019 and 2020 was globally more pronounced than during the 2008–2009 Great Recession. Particularly, women have been disproportionately hit by job losses. The health and well-being of women, children and adolescents, which are directly influenced by household income, was further compromised. COVID-19 caused severe disruptions to sexual, reproductive, maternal, newborn and child health services.

A critical indirect impact on the well-being of women, children and adolescents is also mediated by phenomena, such as family breakdown, domestic violence, which has increased by 5-fold in some countries, disrespect and poor quality of care, such as routine Caesarean sections for COVID-19 positive women and discouraging breastfeeding, as well as adverse effects on mental health in pregnancy and post-partum.²⁵ Emerging data shows that during the COVID-19 pandemic, violence against women and girls, and particularly domestic violence has intensified, taken that security, health and money worries heighten tensions and strains are accentuated by cramped and confined living conditions.²⁷ Governments should strengthen data collection to design long-term strategies, develop gender-equity approaches and incorporate psychosocial support in policies and programmes.

9 | IMPACT AND RESILIENCE IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

Since the onset of the COVID-19 pandemic, coverage of lifesaving health interventions for women, children and adolescents especially in low-income and middle-income countries has considerably dropped. Declines in health service use during the COVID-19 pandemic could have important effects on population health. For individuals living in low-income and middle-income countries, the acute stress of a pandemic occurs within an already much more stressful living situation characterised by significant poverty, thus worsening the effects of stress on perinatal health with potential detrimental downstream consequences.²⁸

The public health objectives of COVID-19 response included slowing and stopping transmission, preventing outbreaks and delaying spread, providing optimised care for all patients, especially the seriously ill, as well as minimising the impact on health systems, social services and economic activity. The WHO and UNICEF provided guidance on community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic. The main purposes in low-income and middle-income countries were to balance the demands of responding directly to COVID-19, while maintaining essential health service delivery and mitigating the risk of system collapse. Governments tried to establish simplified purpose-designed governance and coordination, identify context-relevant essential services, optimise service delivery settings and platforms and establish effective patient flow.

Despite efforts to maintain health services, disruptions of varying magnitude and duration were found in low-income and middle-income countries, with no clear patterns by country, income group or pandemic intensity. Disruptions in health services often preceded COVID-19 waves. Countries must plan to compensate for missed healthcare during the current pandemic and invest in strategies for better health system resilience for future emergencies.²⁹

10 | COVID-19 AND HEALTH EQUITY AND JUSTICE

COVID-19 has widened health, societal and economic inequities. In some countries, young girls are unequally treated in several ways, including poorer nutrition, less expenditure on healthcare and lower immunisation rates. The default in healthcare and health research is a male bias. Many diagnostic tests and treatments are based on data from men. Women have been systematically under-represented in medical research; pregnant and breastfeeding women to an even greater extent. Potential explanations include patriarchal societies, fear of litigation, paternalism, added costs, lack of enabling legislation and an under-representation of women in senior research roles.

COVID-19 has widened indirect inequity against women. Men have greater mortality from COVID-19, but women are more adversely indirectly impacted through reallocation of resources and priorities, including sexual and reproductive health services, increase in unpaid care work, increase in gender-based violence, and increase in food, employment and financial insecurity.²⁷

The lack of timely evidence on the safety and effectiveness of the SARS-CoV-2 vaccine in pregnant and lactating women has shifted responsibility from research sponsors and regulators and placed the burden of decision-making upon the woman and her healthcare advisor. In the future, vaccine developers are recommended to mandate plans that describe the development pathway for new vaccines and medicines, which specifically address the needs of pregnant and lactating women.³⁰

11 | CONCLUSIONS

The COVID-19 pandemic hit swiftly and globally and its aftermath is expected to be long-lasting. Medical, psychological, social and financial consequences of the pandemic are already acknowledged. Significant progress has been made in the field of perinatal COVID-19, still, many issues remain unclear. There is the heterogeneity of data and unresolved questions due to differences in study design and methodologies, biological, ethnic and genetic differences among populations, multi-country environmental and climate indicators and the ongoing pandemic, which daily opens new scenarios for study. Preventive protocols anticipating the medical, social and psychological effects on current and future parents and their offspring need to be implemented, since COVID-19-related outcomes may impact the next generation long after the pandemic itself has been resolved.

ACKNOWLEDGEMENTS

The authors are grateful to the Symposium speakers whose presentations (in brackets) formed the basis for the 10 updated by the authors' sections: Prof. GC Di Renzo, Italy (3), Prof. E. Schleussner, Germany (5), Prof. V. Fanos, Italy (6), Prof. M. Hanson, United Kingdom (7), Dr F. Bustreo, Switzerland (8), Prof. M. Temmerman, Belgium/Kenya (9) and Prof. N. Modi, United Kingdom (10). Chapters 1, 2 and

4 were presented by the authors (Prof. A. Malamitsi-Puchner, Prof. V. Papaevangelou and Prof. D.D. Briana, respectively, all Greece). The authors would also acknowledge the chairpersons at the Symposium Prof. C. Speer, Germany, Prof. G. Visser, the Netherlands and Prof. H. Lagercrantz, Sweden, for their constructive comments.

FUNDING INFORMATION

This study did not receive any specific funding.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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How to cite this article: Briana DD, Papaevangelou V & Malamitsi-Puchner A Action is needed to tackle the clinical, psychological and socioeconomic impact of perinatal COVID-19. *Acta Paediatr.* 2022;00:1-6. <https://doi.org/10.1111/apa.16513>