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EDITORIAL

Neonates in the COVID-19 pandemic

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The coronavirus disease 2019 (COVID-19) pandemic has predominantly affected adults of higher age groups, and the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on infants and neonates appears to be small. While we are gathering emerging evidence on the exact SARS-CoV-2 disease process, intrauterine or perinatal transmission of SARS-CoV-2 remains ambiguous,[1] and vertical transmission has yet to be proven although viral RNA by reverse transcription polymerase chain reaction has been found in placental membranes and breast milk.[2–5] In contrast, breast milk of mothers who contracted COVID-19 can provide antibodies against SARS-CoV-2.[6,7] There are rare case reports of infected infants, the majority of whom were asymptomatic, and symptomatic late-onset viral sepsis has so far only been reported in a 3-week-old infant and a 26-week preterm infant.[8–12] However, longer-term effects of perinatal exposure or sequelae from apparent or occult neonatal COVID-19 are yet unknown and warrant careful monitoring. In response to the sudden pandemic, a wide variation in recommendations for the management of infants born to mothers who are SARS-CoV-2 positive can be found in the literature. For example, the recommendations (1) for careful assessment of the need for personal protective equipment during newborn stabilisation,[13,14] (2) for isolation of 2 weeks of an infant born to an affected mother, and (3) for the allowance of breastfeeding with precautions all vary widely.[15–17]

We recently published an international comparison of guidelines on COVID 19 in neonates to inform the community of neonatologists about differences in management, which could possibly improve outcomes for newborns and their families.[18] This collaboration encompassed 20 countries from 6 continents and compared national and local guidelines on the management of neonates in the early COVID pandemic. We highlighted that no clear-cut guidance on immediate delivery room management was given and that most recommendations suggested asymptomatic infants be not separated from their mother and could be breastfed with hygiene precautions. Important differences emerged that were not explained by the phase of the pandemic at the time of the survey. There were distinct differences in viral testing, advice for personal protective equipment use and family visits. The report highlights how, in the face of a pandemic like COVID-19, rapidly available, consensus-based international, real-time information exchange could better inform local guideline formation and implementation.

However, while few infants suffer relevantly from COVID-19, the "para-COVID" effects are felt prominently in many neonatal intensive care units (NICUs) and have significant collateral effects on the quality of care for neonates. The resources (financial, physical space, healthcare workers, ventilators) diverted to face the COVID-19 epidemic in the adult services strained perinatal and other NICU services. The restriction to parent visiting has potentially significant impact on parental attachment and well-being with secondary effects on infant physical and mental health.[19] Healthcare workers globally (n = 714) reported a 90% increase in stress related to the pandemic.[20] Sufficient resources to support the psychological impacts are required to protect families and healthcare workers. This pandemic has also highlighted major social disadvantages and inequalities in healthcare resources. Global concerns about maternal and neonatal health in countries with limited resources[21,22] due to further shrinking of resources and illness in healthcare providers have been highlighted.

Positive side effects of the pandemic include the rapid development of virtual communication in many NICUs for parents to ensure families are supported and to allow social distancing. Virtual communication can improve extended family involvement in the early NICU period and may reduce the financial burden of illness for families. In addition, international collaborations and interactive conferences have flourished in the past few months.[23] The value of registries and longitudinal follow-up have been recognised and rapidly established at national and international levels[24]: ROI COVID-19 National Register: PAN-COVID Pregnancy and Neonatal outcomes registry (UK); UKOSS COVID-19 in Pregnancy Study (UK); COVI-PREG Registry (Switzerland), OTIS/MotherToBaby Study (USA); Pregnancy Coronavirus Outcomes (PRIORITY) Registry (USA); National Perinatal COVID-19 (NPC-19) registry, American Academy of Pediatrics; CHOPAN Registry (Coronavirus Health Outcomes in Pregnancy and Neonates) – Australian Outcomes Registry; INNSIN Covid-19 (Italian Neonatal Network of Italian Society of Neonatology - Covid-19); EPICENTRE (ESPNIC Covid pEdiatric Neonatal Registry); Spanish Neonatal Society Registro Covid SENeo. The UKOSS initiative has already published their findings showing the relatively low rate of positive tests (5%) in neonates born to women who were SARS-CoV-2 positive.[25]

Reasons for the disparity in serious disease between newborn, children and older adults are not fully understood, although differences in immune function have been described.[26–28] Decreased angiotensin-converting enzyme 2 levels in the nasopharyngeal epithelium and less vigorous interleukin-6 responses during SAR-CoV-2 infection may contribute to the clinical picture.[29] In contrast to the relatively naive neonatal immune system, older adults have an altered response to inflammatory stimuli termed "inflammaging" and thymic involution.[30] However, older children are not immune to the effects of SAR-CoV-2 and may present with Multi-system Inflammatory Syndrome (MIS-C), a condition typically occurring 4–6 weeks post-acute SAR-CoV-2 infection with a spectrum of illness similar to Kawasaki's disease or Toxic Shock syndrome, in some cases leading to shock and multiorgan failure.[31]

Among the many lessons in the management of adults with COVID-19, like using prone positioning for ventilation, the targeted use of surfactant, immune modulation to reduce organ injury by use of dexamethasone and virtual visiting, there are major similarities with neonatal intensive care. As a major positive, the example of the UK-wide RECOVERY trial might be highlighted (recoverytrial.net). This national mega-trial, a collaborative effort between physicians from a wide range of specialities, was set up in ground-breaking speed of only 9 days from concept to first patient inclusion (ISRCTN50189673). It is already the largest ever multi-centre, randomised controlled trial, including 176 centres and patients of all ages, including especially vulnerable populations such as

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pregnant women and children (https://www.recoverytrial.net/news/first-patient-a-child-receives-convalescent-plasma-through-recovery-the-dedicated-covid-19-treatment-trial). The hope is that with the International Neonatal COIVD-19 Consortium such trials can be rapidly developed and extend globally.

Looking ahead, future interdisciplinary learning and collaboration between critical care groups from adults, paediatric and neonatal intensive care may have significant benefits for patients of all age groups. Thus far, the speed of national and international collaboration has been dramatic and it needs to continue to ensure a rapid response, especially as the next pandemic or disaster may disproportionately affect neonates. There is a dire need for supporting a Neonatal International Collaborative Group to promote information exchange for informed local implementation of all aspects of neonatal care. Our aspiration is to develop and maintain an international neonatal collaborative working group on neonatal disaster preparedness. The Collaboration started by Lavizzari and colleagues has already expanded from the initially included 20 countries from 6 continents to >90 collaborating countries worldwide. With such an engaged workforce, our aim is to develop early warning and rapid, evidence-based response systems for future regional and/or global disasters and to develop a multisite registry database.

Neonatal Registries:

- ROI COVID-19 National Register (https://www.ucc.ie/en/npec/roicovid-19study/);
- PAN-COVID Pregnancy and Neonatal outcomes registry (UK) (https://pan-covid.org);
- UKOSS COVID-19 in Pregnancy Study (UK) (https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy);
- COVI-PREG Registry (Switzerland) (https://www.chuv.ch/fr/dfme/dfme-home/recherche/femme-mere/materno-fetal-and-obstetrics-research-unit-prof-baud/covi-preg/);
- OTIS/ MotherToBaby Study (USA) (https://mothertobaby.org/ongoing-study/coronavirus-covid-19/);
- Pregnancy Coronavirus Outcomes (PRIORITY) Registry (USA) (https://priority.ucsf.edu/);
- National Perinatal COVID-19 (NPC-19) registry, American Academy of Pediatrics (https://services.aap.org/en/community/aap-sections/sonpm/in-the-spotlight/);
- CHOPAN Registry (Coronavirus Health Outcomes in Pregnancy and Neonates) – Australian Outcomes Registry (https://www.neonatalcovid19study.com);
- INNSIN Covid-19 (Italian Neonatal Network of Italian Society of Neonatology - Covid-19) (https://www.sin-neonatologia.it);
- EPICENTRE (ESPNIC Covid pEdiatric Neonatal Registry) (Eur J Pediatr. 2020 May 22;1–8); Spanish Neonatal Society Registro Covid SENeo (https://www.se-neonatal.es/~josepr23/sociedades/SENEOv1/index.php/registro-covid-seneo).

AUTHOR CONTRIBUTIONS

E.J.M., together with C.K., J.P., J.A.F.Z., A.L., F.M., C.F.B. and C.C.R., produced the first draft of the manuscript. All collaborators were included on the completion of the manuscript.

ADDITIONAL INFORMATION

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THE INTERNATIONAL NEONATAL COVID-19 CONSORTIUM

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