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Editor: Jon Genuneit

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DOI: 10.1111/pai.13302

Postnatal SARS-CoV-2 infection and immunological reaction: A prospective family cohort study

To the Editor,

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears milder in children, but little is known about neonates and about the chains of infections after delivery.[1-3] When in early March 2020 a midwife in our large maternity and perinatal center returned from vacation in Ischgl, Austria, she triggered a COVID-19 outbreak affecting 36 midwives, nurses, and doctors. We reported previously on the successful containment of this outbreak and characterized the clinical symptoms and immunoglobulin development in staff members exposed to SARS-CoV-2.[4,5]

Here, we present the data of all deliveries with varying degrees of unprotected parental contact with SARS-CoV-2-infected personnel during the first, pre-containment, week of the outbreak. Of the 66 families concerned, 61 consented to a prospective study (University of Regensburg institutional review board ID 20-1791-10) involving serial symptom interview, serial SARS-CoV-2 screening in throat-rinsing fluid (parents) and feces (infants), and serum IgA and IgG antibody studies (parents and infants) 4-5 weeks postpartum. Eighteen families had extensive unprotected contact with infected staff lasting >15 minutes at < 1.5 meters distance (Robert Koch Institute [RKI] risk category I). These families had their first SARS-CoV-2 test in the first week after delivery; they were quarantined for ≥2 weeks after discharge home and received weekly study visits. The remaining 43 less exposed families received only two visits.

We tested for SARS-CoV-2 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for N2 and E gene (Xpert© Xpress SARS-CoV-2, Cepheid) and for serum IgA and IgG antibodies

The peer review history for this article is available at https://publons.com/publon/10.10.1111/pai.13302.

*The copyright line for this article was changed on 23 October 2020 after original online publication.

(EUROIMMUN AG) as previously published.[5] In addition, to verify the antibody responses we performed a second antibody assay in serum and breast milk, which uses a recombinant protein representing the nucleocapsid antigen for determination of all kind of antibodies against SARS-CoV-2 following the manufacturer's instructions (Elecsys Anti-SARS-CoV-2, Roche Diagnostics). According to the manufacturer's recommendations for both antibody assays from EUROIMMUN and Roche Diagnostics, a cutoff index of <1.0 was considered non-reactive (negative for anti-SARS-CoV-2 antibodies) and a value ≥1.0 reactive (positive).

One or both parents from 16 families reported symptoms suggestive of a SARS-CoV-2 infection within 2 weeks postpartum (Table 1). Three of their infants (all spontaneous births) displayed non-specific signs of infection similar to late-onset sepsis, including fever, dyspnea, and compromised circulation leading to admission to our neonatal intensive care unit, at days of life 5 (ID 3), 10 (ID 7), and 26 (ID 1), resolving within few days (Figure 1). Blood cultures and tests for non-SARS-CoV-2 viruses remained negative. Although families with symptoms did not differ in baseline characteristics from those without (n = 45), risk category I families tended to be at higher symptom risk (Table 1).

Five of the 16 families reporting mild COVID-19-compatible symptoms actually contracted COVID-19 based on the RT-PCR and antibody evidence (Figure 1). One of the three symptomatic neonates were RT-PCR-positive and one asymptomatic neonate. Surprisingly, neither the three neonates tested positive for SARS-CoV-2 nor the uninfected newborns had elevated or even borderline antibodies. In addition, three parents of the three families tested positive for SARS-CoV-2 by RT-PCR within the first week after infection (mother ID1, father ID3, and father ID7) had symptoms but remained negative in both antibody tests performed, EUROIMMUN and Roche Diagnostics. Of the symptoms prospectively recorded in adults, only anosmia appeared COVID-19-specific (Figure 1). Only one mother (ID3) produced IgG-positive breast milk (Table 2). Two neonates, one asymptomatic and one symptomatic (ID4 and ID7, respectively), excreted virus in feces for weeks (Figure 1).

Differences in neonatal disease onset timing, between days of life 5 and 26, reflect different chains of intra-family infection. Due to our unique study setting, antepartum infections can be excluded. Albeit we cannot exclude completely the risk of vertical infection via breast milk, much more likely is postnatal infection through horizontal transmission. While separation of the newborn from the COVID-19-suspected or COVID-19-proven mother would theoretically lower infection risk as, for example, suggested by China consensus guidelines,[6] we kept our practice from before the outbreak supporting skin-to-skin care, rooming-in, and breastfeeding for infants born to mothers with COVID-19 in line with the recommendations from the WHO.[7] The important hygiene changes from the time before the COVID-19 outbreak and now are the various protection measures around the mother-infant dyad, including screening of all pregnant women admitted to the maternity hospital and isolation until SARS-CoV-2 test is negative, surgical face masks for all personnel and patients, and proper personal protective equipment when working with patients under investigation for SARS-CoV-2 or for confirmed cases as explained in detail elsewhere.[8] The outbreak coincided with the seasonal flu peak ultimately responsible for most recorded symptoms. Indeed, the coincidence blurred initial pandemic awareness, with some staff and parents already wearing surgical face masks for seasonal flu protection.

Our finding that not all RT-PCR-positive family members produced antibodies against SARS-CoV-2 is in line with previous reports from us and others, describing a match rate of only 70%-80% between RT-PCR and antibody results in COVID-19 patients.[5,9] These findings may indicate that an relevant amount of COVID-19 patients, including neonates, does not develop a humoral response to SARS-CoV-2. If these data are corroborated by further investigations, there is limited value in determining antibodies against SARS-CoV-2. Furthermore, the role of the humoral immune response in fending off SARS-CoV-2 requires additional discussions which may have far-reaching implications for gauging the value of newly developed vaccines.

Together, like their parents, newborn infants can contract COVID-19 in the first weeks postpartum and their symptoms may

TABLE 1 Baseline characteristics

		Study families (n = 61)		
	All (n = 66)	COVID-19-compatible symptoms (n = 16)	No symptoms (n = 45)	*P*
Maternal age, y, M (range)	30 (17-42)	32 (24-36)	30 (17-42)	0.774
Gestational age, wk, M (range)	39.3 (31.9-41.7)	39.3 (34.9-41.7)	39.3 (31.9-41.4)	0.594
Mode of delivery, C-section, n (%)	21 (32)	4 (25)	16 (36)	0.544
RKI risk category I, n (%)	18 (27)	7 (44)	11 (24)	0.203

Abbreviations: C-section, cesarean section; M, median; RKI, Robert Koch Institute (German public health authority).

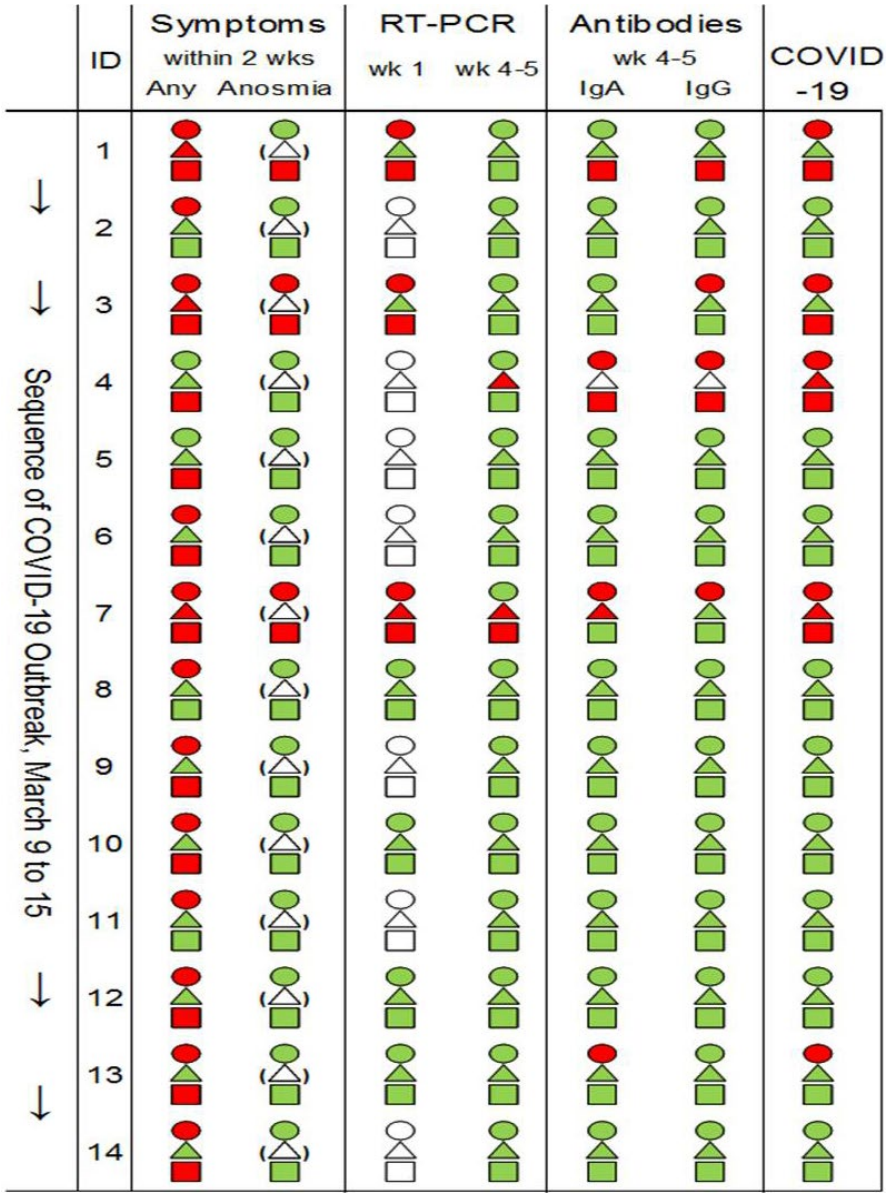

FIGURE 1 Fourteen families (ID 1-14) reporting COVID-19-compatible symptoms within 2 wk postpartum, listed by birth order between March 9 and 15, 2020, and screened twice (two further symptomatic families were unavailable for the second screening). Families in Robert Koch Institute risk category I exposed to prolonged and close unprotected contact (>15 min at <1.5 meters distance) with infected staff were screened for SARS-CoV-2 by RT-PCR 1 wk and 4-5 wk postpartum. All other families were screened once only, at 4-5 wk. Circle, mother; triangle, infant; rectangle, father; red, positive; green, negative; clear, not done; brackets, not applicable; weeks, weeks; RT-PCR, reverse transcriptase-polymerase chain reaction [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Clinical findings [n (%)] in families with COVID-19-compatible symptoms (n = 16)

	Mothers	Fathers	Infants
Any COVID-19-compatible symptoms	14 (88)	13 (81)	3 (19)
Cough	4 (25)	5 (31)	1 (6)
Sore throat	9 (56)	9 (56)	0 (0)
Rhinorrhea	4 (25)	8 (50)	2 (12)
Shortness of breath	1 (6)	3 (19)	2 (12)
Fever	1 (6)	0 (0)	3 (19)
Fatigue	4 (25)	6 (38)	2 (12)
Myalgia	3 (19)	3 (19)	—
Headache	3 (19)	2 (12)	—
Anosmia	2 (12)	3 (19)	—
Admission to NICU	0 (0)	0 (0)	3 (19)

Abbreviation: NICU, neonatal intensive care unit.

show similarities with late-onset sepsis. In adults, anosmia may differentiate mild COVID-19 from common flu. Finally, additional studies are needed to better understand the humoral immune response against SARS-CoV-2.

AUTHOR CONTRIBUTIONS

Julia Preßler: Conceptualization (supporting); Data curation (equal); Investigation (equal); Project administration (supporting); Writing-original draft (equal). **Sara Fill Malfertheiner:** Investigation (equal); Project administration (equal); Supervision (supporting); Writing-review & editing (supporting). **Michael Kabesch:** Conceptualization (equal); Methodology (equal); Resources (equal); Writing-original draft (equal). **Heike Buntrock-Doepke:** Data curation (supporting); Project administration (equal); Supervision (supporting); Writing-review & editing (supporting). **Sebastian Häusler:** Investigation (supporting); Resources (supporting); Writing-review & editing (supporting). **Andreas Ambrosch:** Data curation (supporting);

Investigation (supporting); Methodology (supporting); Project administration (supporting); Resources (supporting); Writing-review & editing (supporting). **Sven Wellmann:** Conceptualization (lead); Project administration (equal); Resources (equal); Supervision (lead); Writing-original draft (lead).

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