Journal of Tropical Pediatrics, 2020, 0, 1–14
doi: 10.1093/tropej/fmaa059
Original Paper

Clinical Features and Outcome of SARS-CoV-2 Infection in Neonates: A Systematic Review

Shashi Kant Dhir DM,* Jogender Kumar DM,*
Jitendra Meena DM, *and* Praveen Kumar DM

Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India
*These authors contributed equally to this work.
Correspondence: Praveen Kumar, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. Tel: 172-2755318, 2755308. Fax: 172-2744401. E-mail: drpkumarpgi@gmail.com

ABSTRACT

Objective: The objective of this study is to systematically synthesize the currently available literature on various modes of transmission (congenital, intrapartum, and postpartum), clinical features and outcomes of SARS-CoV-2 infection in neonates.
Methods: We conducted a comprehensive literature search using PubMed, EMBASE, and Web of Science until 9 June 2020. A combination of keywords and MeSH terms, such as COVID-19, coronavirus, SARS-CoV-2, 2019-nCoV, severe acute respiratory syndrome coronavirus 2, neonates, newborn, infant, pregnancy, obstetrics, vertical transmission, maternal–foetal transmission and intrauterine transmission, were used in the search strategy. We included studies reporting neonatal outcomes of SARS-CoV-2 proven pregnancies or neonatal cases diagnosed with SARS-CoV-2 infection.
Results: Eighty-six publications (45 case series and 41 case reports) were included in this review. Forty-five case series reported 1992 pregnant women, of which 1125 (56.5%) gave birth to 1141 neonates. A total of 281 (25%) neonates were preterm, and caesarean section (66%) was the preferred mode of delivery. Forty-one case reports describe 43 mother-baby dyads of which 16 were preterm, 9 were low birth weight and 27 were born by caesarean section. Overall, 58 neonates were reported with SARS-CoV-2 infection (4 had a congenital infection), of which 29 (50%) were symptomatic (23 required ICU) with respiratory symptoms being the predominant manifestation (70%). No mortality was reported in SARS-CoV-2-positive neonates.
Conclusion: The limited low-quality evidence suggests that the risk of SARS-CoV-2 infections in neonates is extremely low. Unlike children, most COVID-positive neonates were symptomatic and required intensive care. Postpartum acquisition was the commonest mode of infection in neonates, although a few cases of congenital infection have also been reported.

KEYWORDS: breast milk, congenital infection, COVID-19, neonates, pregnancy

INTRODUCTION

Novel coronavirus infection (later termed as COVID-19) was declared a global pandemic on 11 March 2020 and as of 12 June 2020, the number of confirmed cases has reached 7 410 510 and 418 294 (5.6%) deaths have been reported worldwide [1]. A significant number of pregnant females are also affected, as they are equally susceptible to SARS-CoV-2 infection [2]. Neonatal SARS-CoV-2 infections are rare, and till now a handful of cases are

reported. Although the newborns are considered at risk for vertical and postpartum horizontal transmission, there is a dearth of data on the clinical features, outcome, mode of transmission and mode of delivery for neonates. Also, there is uncertainty about the transmission of the SARS-CoV-2 virus through the placenta and breast milk [3–9].

Therefore, we performed this systematic review to synthesize the currently available literature on various modes of transmission (congenital, intrapartum and postpartum), clinical features and outcomes of SARS-CoV-2 infection in neonates.

MATERIALS AND METHODS

Search strategy

This study was conducted following the Meta-analysis Of Observational Studies in Epidemiology guidelines [10]. A predefined search strategy was developed, and three investigators (S.K.D., J.M., and J.K.) independently performed a literature search in MEDLINE, EMBASE and Web of Science for the original articles published between 1 December 2019 and 9 June 2020. Terms used for literature search were COVID-19, coronavirus, SARS-CoV-2, 2019-nCoV, severe acute respiratory syndrome coronavirus 2, neonates, newborn, infant, pregnancy, obstetrics, vertical transmission, maternal–foetal transmission, and intrauterine transmission. Specific search strategies were created for each electronic database separately, by using the MeSH terms, Emtree terms and terms described above (Supplementary Table S1). The electronic search was also supplemented by a hand search of bibliography of the included studies and relevant review articles. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [11]. No language restrictions were used.

Study selection

A predefined set of criteria was used for the assessment of the eligibility of the studies for this systematic review. Studies enrolling neonates and/or pregnant mothers and reporting data on COVID-19 testing of the neonates were considered eligible for the review. Initially, two researchers (J.M. and S.K.D.) independently screened the title and abstract for the eligibility. Later three authors (S.K.D., J.M. and J.K.) examined the full-text articles for inclusion and exclusion criteria. Studies were included if they met the following criteria: (i) studies reporting the neonatal outcome of pregnancy with RT-PCR proven SARS-CoV-2 infection, (ii) studies reporting clinical manifestations, disease severity, laboratory investigations and outcome of RT-PCR proven SARS-CoV-2 infection in neonates (postnatal age $<$ 29 days for the term and postmenstrual age up to 44 weeks for preterm neonates), (iii) all types of study designs: cohort, cross-sectional studies, case–control studies, case series and case reports. Correspondences or letters fulfilling the above criteria were also included. We excluded: (i) studies with term neonates aged more than 28 days and preterm neonates with postmenstrual age more than 44 weeks, (ii) studies reporting COVID-19-positive pregnancy without any neonatal outcomes, (iii) studies not reporting the neonatal COVID-19 status, (iv) studies reporting about other serotypes of coronavirus or testing methods other than RT-PCR, (v) narrative or systematic review, (vi) conference proceedings and (vii) editorial, perspective, etc. not meeting the inclusion criteria.

Data extraction and quality assessment

A structured performa was used for the data extraction. Two investigators independently extracted the desired data from the full-text of the eligible studies. The details of extracted data parameters are given in Supplementary Appendix Table S2. The studies published in Chinese language were first translated to English language using Google translation and then the desired data were extracted. Any disagreement between two investigators was resolved through discussion with the third investigator (J.K.). A researcher (J.K.) independently rechecked the extracted data for its accuracy and completeness. The quality of the included studies in this systematic review was assessed using the Newcastle Ottawa scale [12]. Two investigators (S.K.D. and J.K.) independently assigned an overall risk of bias to each eligible study, and if they disagreed, another researcher (J.M.) was involved to resolve the discrepancy.

Data synthesis and statistical analysis

We summarized the relevant clinical details of the neonates and pregnant mothers described in the included studies. Clinical details, demographics, the time of doing RT-PCR for SRS-CoV-2 infection in neonates and outcomes of the SARS-CoV-2-positive neonates were summarized separately. Mother was considered to have SARS-CoV-2 (COVID-19) infection only if the RT-PCR from nasopharyngeal/oropharyngeal swab was positive [13]. Neonate was considered to have COVID-19 infection if the RT-PCR from nasopharyngeal/oropharyngeal swab from infant or blood from neonate/umbilical cord or amniotic fluid or tissue sample from the foetal side of the placenta was positive for SARS-CoV-2 [13]. The neonates with SARS-CoV-2 infection were further classified to characterize the mode of transmission (congenital, acquired intrapartum and acquired postpartum) [13]. Percentages and mean/median values were calculated to describe categorical and continuous variables, respectively. SPSS v23 was used for statistical analysis.

RESULTS

Study selection and characteristics

We found a total of 1313 records. The detailed process of selection of final included studies for this systematic review is described in Fig. 1. After removing 741 duplicates, 578 articles were screened for

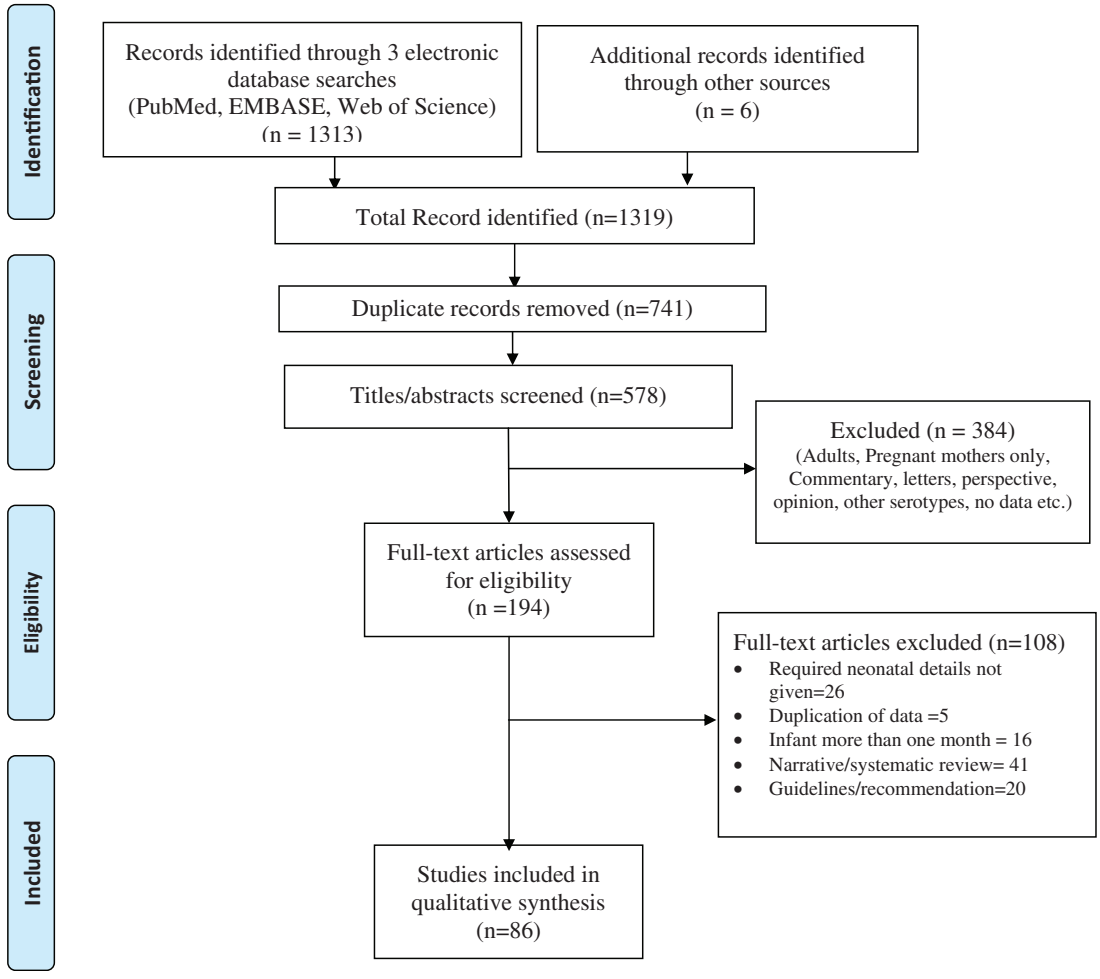

Fig. 1. PRISMA flow diagram.

Table 1. Details of included studies (case series and cohort)

Author	Date of publication	Country	Study design	Study quality	Pregnant women (*n*)	Gestational age (weeks)	Vaginal delivery (total delivered)	Live births (*n*)	Preterm, *n* (%)	Birth weight (g)	Neonates tested(*n*)	COVID-positive neonates
Breslin *et al.* [14]	9 April 2020	USA	Retrospective	Fair	43	37 (32–38)[a]	10 (18)	18	1 (5)	–	18	0
Buonsenso *et al.* [15]	21 April 2020	Italy	Observational	Poor	7	8–37[b]	0 (2)	2	1 (50)	2300, 3390	2	2
Campbell *et al.* [46]	26 May 2020	USA	Case series	Poor	30	Term	20 (30)	30	0	3370 (621)[c]	30	0
Cao *et al.* [16]	10 April 2020	China	Retrospective	Fair	10	33–40[b]	2 (10)	11	4 (36)	2050–3800[b]	4	0
Chen *et al.* [3]	12 February 2020	China	Retrospective	Fair	9	36–39[b]	0 (9)	9	4 (44)	1880–3730[b]	6	0
Chen *et al.* [17]	16 March 2020	China	Case series	Poor	4	37–39[b]	1 (4)	4	0	3050–3800[b]	3	0
Chen *et al.* [18]	28 March 2020	China	Observational	Fair	5	38–41[b]	3 (5)	5	0	3235–4050[b]	5	0
Chen *et al.* [19]	17 April 2020	China	Retrospective	Poor	118	–	5 (68)	68	14 (21)	–	8	0
Chen *et al.* [20]	10 March 2020	China	Case series	Poor	17	–	0 (17)	17	3 (18)	–	0	0
Chen *et al.* [21]	08 May 2020	China	Case series	Poor	3	–	0 (2)	2	1 (33)	–	2	0
Fan *et al.* [22]	17 March 2020	China	Case series	Fair	2	36–37[b]	0 (2)	2	0	2890, 3400	2	0
Ferrazzi *et al.* [23]	07 April 2020	Italy	Retrospective	Fair	42	–	24 (42)	42	11 (26)	840–4040[b]	42	3
Govind *et al.* [24]	07 May 2020	England	Observational	Fair	9	36.8 (27–39)[a]	1 (9)	9	7 (78)	–	9	1
Hernández *et al.* [47]	05 June 2020	Spain	Case series	Good	3	39	– (3)	3	1 (33)	1135–3700[b]	3	3
Hantoushzadeh *et al.* [25]	24 April 2020	Iran	Case series	Fair	9	32.7 (28–38)[a]	0 (5)	6	5 (83)	1180–3200[b]	6	1
Hirshberg *et al.* [26]	01 May 2020	USA	Case series	Fair	5	25–31[b]	0 (3)	3	3 (100)	1500–2110	3	0
Huang *et al.* [27]	08 May 2020	China	Retrospective	Poor	8	28–39[b]	1 (6)	6	3 (50)	1520–4200[b]	6	0
Kayem *et al.* [44]	31 May 2020	France	Case series	Poor	617	22–37[b]	94 (181)	190	50 (28)	–	190	2
Khan *et al.* [28]	19 March 2020	China	Case series	Fair	3	34–39[b]	3 (3)	3	1 (33)	2890–3730[b]	3	0
Khan *et al.* [48]	27 March 2020	China	Case series	Fair	17	35–41[b]	0 (17)	17	3 (18)	2300–3750[b]	17	0
Knight *et al.* [49]	08 June 2020	UK	Case series	Fair	427	38 (36–40)[a]	106 (253)	259	63 (24)	–	259	12
Li *et al.* [45]	30 March 2020	China	Case–control	Good	16	38 (0.2)[a]	3 (16)	17	4 (23)	3066 (560)[c]	3	0
Liao *et al.* [29]	29 April 2020	China	Retrospective	Good	10	38 (1.43)[a]	10 (10)	10	1 (10)	3283 (449)[c]	7	0
Liu *et al.* [30]	27 February 2020	China	Retrospective	Fair	13	32–38[b]	0 (10)	10	7 (70)	–	9	0
Liu *et al.* [31]	17 March 2020	China	Observational	Fair	10	38 (1.5)[c]	1 (10)	10	2 (20)	3293 (425)[c]	10	0
Liu *et al.* [32]	07 March 2020	China	Retrospective	Poor	15	37 (1)[c]	1 (11)	11	–	–	11	0
Martinez-Perez *et al.* [50]	08 June 2020	Spain	Case series	Poor	82	–	41 (82)	82	25 (30)	910–4750[b]	82	5
Ochiai *et al.* [51]	04 June 2020	Japan	Case series	Poor	52	38	0 (2)	2	0	3715, 2805	2	0
Pereira *et al.* [5]	22 May 2020	Spain	Observational	Good	60	32 (5–41)[a]	18 (23)	23	2 (9)	–	23	0
Pierce-Williams *et al.* [33]	04 May 2020	USA	Cohort	Good	64	34 (4.2)[c]	8 (32)	32	19 (59)	2403 (858)[c]	33	1
Qadri and Mariona [52]	20 May 2020	USA	Case series	Poor	16	22–40[b]	8 (12)	12	1 (8)	2830–4215[b]	12	0
Qiancheng *et al.* [34]	22 April 2020	China	Retrospective	Fair	28	38 (36–39)[a]	5 (22)	23	1 (4)	2915–3390[b]	22	0
Salvatori *et al.* [35]	15 May 2020	Italy	Case series	Fair	2	39–41[b]	– (2)	2	0	3120, 4440	2	2
Sun *et al.* [36]	19 April 2020	China	Case series	Fair	3	31–37[b]	0 (3)	3	2 (67)	–	3	1
White *et al.* [53]	04 June 2020	USA	Case series	Good	3	39	2 (3)	3	0	–	2	2
Wu *et al.* [37]	05 May 2020	China	Case series	Fair	13	5–38[b]	1 (5)	5	2 (40)	2300–3910[b]	5	0
Xu *et al.* [38]	28 April 2020	China	Retrospective	Fair	5	34–39[b]	4 (5)	5	2 (40)	2450–3760[b]	5	0
Yan *et al* [39]	17 April 2020	China	Retrospective	Good	116	38.4 (37–39)[a]	14 (100)	100	21 (21)	3108 (526)[c]	86	0
Yang *et al* [40]	5 April 2020	China	Prospective	Good	7	36–38[b]	0 (7)	7	4 (57)	2096 (660)[c]	6	0
Yu *et al.* [41]	24 March 2020	China	Retrospective	Fair	9	39 (37–41)[a]	0 (7)	7	0	3000–3500[b]	3	1
Zeng *et al.* [7]	26 March 2020	China	Prospective	Poor	6	–	– (6)	6	–	–	6	0
Zeng *et al.* [42]	26 March 2020	China	Cohort	Fair	33	–	0(33)	33	4(12)	–	19	3

(continued)

Table 1. (continued)

Author	Date of publication	Country	Study design	Study quality	Pregnant women (*n*)	Gestational age (weeks)	Vaginal delivery (total delivered)	Live births (*n*)	Preterm, *n* (%)	Birth weight (g)	Neonates tested(*n*)	COVID-positive neonates
Zeng *et al.* [54]	21 May 2020	China	Case series	Poor	16	37 (34–41)[a]	4 (16)	12	3 (25)	3175 (478)[c]	16	0
Zhang *et al* [55]	25 March 2020	China	Case series	Good	16	29 (2.9)[c]	0 (10)	10	1 (10)	–	10	0
Zhu *et al.* [43]	10 February 2020	China	Case series	Poor	9	31–39[b]	2 (9)	10	5 (50)	1720–3800[b]	10	0

[a]Median (IQR).
[b]Range.
[c]Mean (SD).

eligibility through titles and abstracts. A total of 384 articles were excluded, and 194 articles were retrieved for full-text assessment. After a thorough screening of full-text articles, 85 (45 case series/cohort and 41 case reports) publications were included for the qualitative synthesis. Quality assessment was done for 45 studies, of which 9 were rated as good, 21 as fair, and 15 of poor quality by the Newcastle Ottawa scale [12].

Clinical details

Forty-five studies [3, 5, 7, 14–55] described 1992 pregnant women with gestation ranging from 5 to 41 weeks. Birth was reported amongst 1125 (56.5%) of these. The mode of delivery was available for 1114 pregnancies, and caesarean section (65%) was more frequent than vaginal delivery. A total of 1141 neonates were born of which, 281 (25%) were preterm (<37 weeks). SARS-CoV-2 testing was done for 1005 (88%) neonates and 39 (3.9%) turned out to be positive on RT-PCR (Table 1). Forty-one case reports [4, 6, 8, 56–93] described 43 mother-baby dyads, of which 16 (37.2%) were preterm (<37 weeks), 9 (21%) were low birth weight (<2500 g) and 27 (62.8%) were born by caesarean section (Table 2). All 43 were tested for SARS-CoV-2 infection using nasopharyngeal or oropharyngeal specimen and 19 neonates (44.2%) have positive RT-PCR for SARS-CoV-2.

We identified a total of 58 SARS-CoV-2 RT-PCR-positive neonates. The clinical details, demographics and outcome of these neonates are described in Table 3. Of these 58 neonates, maternal COVID testing details were available for 53 and all were positive for SARS-CoV-2 infection. The perinatal characteristics and clinical features of SARS-CoV-2-positive neonates are summarized in Table 4. Most of the neonates became symptomatic beyond 24 h of birth. Among term neonates, 10 had onset of symptoms in first week (7 on Day 2 of life itself), 3 each in second and third weeks and 4 in fourth week of life. Except one (Meconium aspiration syndrome), none of these term infants had any other neonatal illness to explain the symptoms. In preterm, only one had symptoms on first day, one on second day and rest five had at or beyond Day 7 of life. Among all COVID-positive neonates, 22 (38%) required ICU admission and 10 (17%) were ventilated (invasive and non-invasive). Separate details for invasive and non-invasive ventilation were not available as most except one [71] did not report it clearly.

The outcome (discharge/death) has been reported for 31 neonates of which 26 have been discharged to home and 5 were still admitted. No mortality has been reported in SARS-CoV-2-infected neonates.

Mode of transmission

To understand the mode of transmission as well as to maintain the uniformity in reporting we classified the SARS-CoV-2-infected neonates into various categories [13]. Of these 58 live-born SARS-CoV-2 cases, 4 (7%) were congenital in origin (2 confirmed, 1 probable and 1 not sure), 41 were acquired in the postpartum period and the remaining 13 neonates could not be classified due to non-availability of complete details.

Table 2. Details of included studies (case reports)

Author	Date of publication	Country	No. of COVID+ mothers	COVID+ neonates (n)	Gestation (weeks)	Birth weight (g)	Mode of delivery	Apgar (1/5 min)	Symptoms
Aghdam *et al.* [56]	1 April 2020	Iran	1	1	–	3460	CS	–	Fever, lethargy, mottling, tachypnoea, RD
Aguilar *et al.* [57]	27 April 2020	Spain	1	1	–	–	–	–	Seizures, Hypertonia, Fever, Watery stools
Alzamora *et al.* [58]	18 April 2020	Peru	1	1	33	2970	CS	6/8	RD, cough
Blauvelt *et al.* [59]	8 May 2020	USA	1	0	28	1880	CS	4/8	HMD, leukopenia, mild acidosis
Carosso *et al.* [60]	14 April 2020	Italy	1	1	37	3120	VD	9/10	Asymptomatic
Cook *et al.* [86]	19 May 2020	UK	–	1	27	–	–	–	Poor feeding, dyspnoea, respiratory failure, shock
De Socio *et al.* [61]	1 May 2020	Italy	1	0	40	–	VD	10/10	Asymptomatic
Fontanella *et al.* [92]	29 May 2020	Netherlands	1	0	40	–	CS	9/9	Asymptomatic
Groß *et al.* [8]	21 May 2020	Germany	2	2	–	–	–	–	Breathing difficulty
Han *et al.* [62]	16 April 2020	Korea	1	1	38	3730	VD	–	Fever, nasal blockage, tachycardia, cough
Iqbal *et al.* [63]	1 April 2020	USA	1	0	39	–	VD	8/9	Asymptomatic
Jain *et al.* [93]	5 June 2020	India	2	0	Term	2865/–	CS	–/–	Asymptomatic/second-asphyxia, shock, ventilated
Kirtsman *et al.* [64]	14 May 2020	Canada	1	1	40	2930	CS	9/9	Hypothermia, feeding difficulty, hypoglycaemia
Kuhrt *et al.* [65]	8 May 2020	England	1	0	32	2190	CS	8/9	Ventilated
Lang *et al.* [6]	8 May 2020	China	1	0	35	–	CS	9/10	Asymptomatic
Lee *et al.* [66]	31 March 2020	Korea	1	0	37	3130	CS	9/10	Asymptomatic
Li *et al.* [67]	5 March 2020	China	1	0	35	–	CS	–	Asymptomatic
Li *et al.* [68]	5 May 2020	China	1	0	35	2700	CS	1/1	Birth asphyxia, died
Li *et al.* [69]	2020	China	1	1	38	–	CS	–	–
Liao *et al.* [70]	26 March 2020	China	1	0	35	–	CS	–	–
Lorenz *et al.* [71]	12 May 2020	Germany	1	1	40	–	VD	9/9	Fever, encephalitis like symptoms, cough
Lowe *et al.* [72]	15 April 2020	Australia	1	0	40	–	VD	9/9	Asymptomatic
Lu *et al.* [73]	23 April 2020	China	1	0	38	3470	CS	9/9	Asymptomatic
Lyra *et al.* [74]	20 April 2020	Portugal	1	0	39	3110	CS	8/9	Asymptomatic
Mehta *et al.* [87]	16 May 2020	USA	1	1	28	925	CS	5/6	Asymptomatic
Munoz *et al.* [75]	22 April 2020	USA	1	1	36	–	–	–	Hypotension, hypothermia, tachypnoea
Peng *et al.* [4]	6 April 20	China	1	0	35	2600	CS	9/10	HMD, tachypnoea, apnoea
Perrone *et al.* [88]	21 May 2020	Italy	1	0	32	–	VD	–	Asymptomatic
Piersigilli *et al.* [76]	7 May 2020	Belgium	1	1	26	960	CS	5/8	HMD, PDA, pneumothorax
Salik and Mehta [89]	25 May 2020	USA	1	1	37	1900	–	–	Tetralogy of Fallot
Sharma *et al.* [77]	20 April 2020	India	1	0	38	–	CS	–	Asymptomatic
Sinelli *et al.* [78]	1 May 2020	Italy	1	1	–	–	VD	9/10	RD
Wang *et al.* [85]	28 February 2020	China	1	0	30	1830	CS	9/10	Asymptomatic
Wang *et al.* [79]	12 March 2020	China	1	1	40	3205	CS	8/9	Vomiting, lymphopenia, deranged LFT
Wang *et al.* [90]	22 March 2020	China	1	1	38	3030	VD	–	Vomiting
Xia *et al.* [80]	17 March 2020	China	1	0	37	3100	CS	9/10	–
Xiong *et al.* [81]	7 April 2020	China	1	0	38	3070	VD	9/10	Asymptomatic
Yilmaz *et al.* [91]	17 May 2020	Turkey	1	0	38	2900	CS	9/10	Asymptomatic
Zamaniyan *et al.*[82]	17 April 2020	Iran	1	1	32	2350	CS	8/9	Fever

(continued)

Table 2. (continued)

Author	Date of publication	Country	No. of COVID+ mothers	COVID+ neonates (n)	Gestation (weeks)	Birth weight (g)	Mode of delivery	Apgar (1/5 min)		Symptoms
Zambrano *et al.* [83]	25 March 2020	Honduras	1	0	32	1500	VD	–	–	
Zhou *et al.* [84]	28 April 2020	China	1	0	37	–	CS	–	–	

CS, caesarean section; HMD hyaline membrane disease; LFT, liver function tests RD, respiratory distress; VD, vaginal delivery.

SARS-CoV-2 secretion in breast milk

A few studies tested breast milk for the SARS-CoV-2 virus and have reported conflicting results [3, 6, 8, 19, 37, 64]. Initial studies did not find any SARS-CoV-2 RNA in breast milk [3, 6, 19, 22, 67, 69]. However, recently few authors reported detection of SARS-CoV-2 in breast milk [8, 37, 64].

DISCUSSION

This review summarizes the perinatal characteristics, clinical features and outcome of RT-PCR proven SARS-CoV-2 infection in neonates. As described previously, the total number of reported paediatric cases is quite less than the adults of which the neonates are just a handful. Most of the reported neonatal infections are acquired in the postpartum period, and the overall prognosis is excellent.

Unlike older children and adults in which most of the infections are clinically asymptomatic, two-thirds of the neonatal cases were symptomatic [94]. As given in results, most of the neonates were clinically well before appearance of symptoms, suggesting that these symptoms are unlikely to be due to the prematurity or other non-COVID illness. Similar to the children and adults, respiratory symptoms were the predominant manifestations in neonates too, however, unlike them, fever was seen in one-fifth of the cases only [94–96]. Like older children, about 10% of the neonates had gastrointestinal manifestations, and the overall prognosis of SARS-CoV-2 infection in neonates is better than adults [94–97]. Although the frequency of SARS-CoV-2-positive neonates is extremely low, a significant proportion of the affected neonates requiring intensive care and mechanical ventilation suggests that the disease in neonates is more severe than older children [96–98].

Although the protective effect of caesarean section against SARS-CoV-2 transmission to neonate lacks evidence and most of the guidelines advise to reserve a caesarean section for obstetric indication only, the proportion of caesarean section was much more than vaginal deliveries [99, 100]. Higher rates for caesarean delivery may be due to either clinician preference or maternal sickness or comorbidities. Due to population-based differences in mode of delivery like Chinese having preference for caesarean section even in non-COVID pregnancies, we analysed the data as per country of origin of the study [101]. Caesarean section rate for COVID-19 pregnancies in China was found to be as high as 86% when compared with 53% in other countries. Also, data suggest an overall preference for caesarean delivery worldwide.

Many studies have highlighted the association of COVID-19 and increased preterm deliveries [5, 23]. In our review also about one-fourth of the neonates were born premature, which is much more than overall global (10.6%) and China's (6.9%) preterm birth rate [102]. The exact reason for the higher preterm birth rate could not be delineated from this review.

Since the beginning of the pandemic, there is a debate about vertical transmission of SARS-CoV-2 infection. Early reports from China suggested that the intrauterine vertical transmission is unlikely [3–6, 9]. However, the detection of antibodies in cord blood and neonate raised concerns [7]. Ideally, to prove a vertical transmission, testing of placental tissue, amniotic fluid before rupture of membranes, umbilical cord blood, neonatal blood in the first 12 h and neonatal throat/nasopharyngeal swab for RT-PCR in the immediate postpartum period are recommended [13]. Initial studies that tested all these

Table 3. Clinical details, mode of transmission and outcome of COVID-positive neonates (n=58)

Author	Neonates (n)	Mother COVID +	MOD	GA (weeks)/ weight (g)	NP swab positive (DOL)	NP swab negative (DOL)	Direct breast feeding	Clinical features	ICU stay	MV	Final outcome	Mode of transmission
Aghdam *et al.* [56]	1	–	CS	Term/3460	15	–	–	Fever, mottling, respiratory distress	Yes	No	Discharged	Postpartum acquired
Aguilar *et al.* [57]	1	–	–	–	26	–	Yes	Seizures, fever, irritability, watery stools	Yes	No	Discharged	Postpartum acquired
Alzamora *et al.* [58]	1	Yes	CS	33/2970	1	–	No	Respiratory distress	Yes	Yes	–	Not assigned[a]
Buonsenso *et al.* [15]	2	Yes	CS	38/3390	15	–	Yes	Asymptomatic	No	No	Discharged	Postpartum acquired
				35/2300	–	1	No	Asymptomatic	No	No	Discharged	Congenital (confirmed)[b]
Carosso *et al.* [60]	1	Yes	VD	37/3120	At birth	3	–	Asymptomatic	No	No	Discharged	Congenital[c]
Cook *et al.* [86]	1	–	–	27/–	56	–	–	Poor feeding, dyspnoea, respiratory failure, shock	Yes	Yes	Admitted	Postpartum acquired
Ferrazzi *et al.* [23]	3	Yes	VD	–	1	–	Yes	Asymptomatic	–	–	–	Not assigned[a]
			CS	–	3	–	Yes	Asymptomatic	–	–	–	Postpartum acquired
			VD	Term/–	3	–	No	GI and respiratory	Yes	Yes	–	Postpartum acquired
Govind *et al.* [24]	1	Yes	CS	38/4165	–	–	No	Desaturation, fever	Yes	Yes	–	Postpartum acquired
Hernández *et al.* [47]	3	Yes	VD	Term/3700	2	10	–	MAS	Yes	Yes	Discharged	Postpartum acquired
		Yes	VD	Preterm/1135	78	84	–	–	Yes	Yes	Discharged	Postpartum acquired
		Yes	VD	Term/3550	6	13	–	Asymptomatic	No	No	Discharged	Postpartum acquired
Groß *et al.* [8]	2	Yes	–	–	4	–	Yes	Respiratory distress	No	No	Discharged	Postpartum acquired
					11	24	Yes	Respiratory distress, hypoxia	–	No	Discharged	Postpartum acquired
Han *et al.* [62]	1	Yes	VD	38/3730	27	–	Yes	Fever, cough, vomiting	Yes	No	Discharged	Postpartum acquired
Hantoushzadeh *et al.* [25]	1	Yes	CS	30/–	7	–	No	Pneumonia	Yes	–	Admitted	Postpartum acquired
Kayem *et al.* [44]	2	Yes	–	–	–	–	–	Asymptomatic/hypoxia	–	–	–	Details not available
Kirtsman *et al.* [64]	1	Yes	CS	35/2930	At birth	7	Yes	Asymptomatic	No	No	Discharged	Congenital (probable)[d]
Knight *et al.* [49] (individual patient details not available)	6	Yes	2 VD, 4 CS	3 preterm 3 Term	<12 h	–	–	–	–	–	–	Not assigned[a]
	6	Yes	2 VD, 4 CS	4 preterm 2 Term	>12 h	–	–	–	1	–	–	Postpartum acquired
Li *et al.* [69]	1	Yes	CS	38/–	3	–	–	Asymptomatic	No	No	Discharged	Postpartum acquired
Lorenz *et al.* [71]	1	Yes	VD	40/–	2	–	–	Lethargy, pneumonia, encephalitis syndrome (fever, seizures, altered sensorium)	Yes	CPAP	Discharged	Postpartum acquired
Martinez-Perez *et al.* [50]	5	Yes	CS	Term/–	10	–	Yes	COVID symptoms	–	–	–	Postpartum acquired
		Yes	CS	Term/–	10	–	Yes	COVID symptoms	–	–	–	Postpartum acquired
		Yes	VD	Preterm/–	1	2	–	Asymptomatic	No	No	–	Not assigned[a]
		Yes	VD	Preterm/–	1	2	–	Asymptomatic	No	No	–	Not assigned[a]
		Yes	CS	–	1	2	–	Asymptomatic	No	No	–	Not assigned[a]
Mehta *et al.* [87]	1	Yes	CS	28/925	3	–	No	Asymptomatic	Yes	No	Admitted	Postpartum acquired
Munoz *et al.* [75]	1	–	–	36/–	17	–	–	Hypotension, tachycardia, hypothermia, tachypnoea	Yes	Yes	Discharged	Postpartum acquired
Piersigilli *et al.* [76]	1	Yes	CS	26/960	7	21	No	HMD, pneumothorax	Yes	Yes	Admitted	Postpartum acquired
Pierce-Williams *et al.* [33]	1	Yes	–	–	2	–	–	Asymptomatic	–	–	Discharged	Postpartum acquired
Salik and Mehta [89]	1	Yes	–	37/1.9	7	13	–	Tet spells, tachypnoea, pneumonia	Yes	Yes	–	Postpartum acquired
Salvatori *et al.* [35]	2	Yes	–	41/4440	18	–	Yes	Asymptomatic	No	No	Discharged	Postpartum acquired
				39/3120	10	–	Yes	Cough, diarrhoea, poor feeding	No	No	Discharged	Postpartum acquired
Sinelli *et al.* [78]	1	Yes	VD	Term/–	2	–	No	Hypoxia, cyanosis, poor sucking	Yes	No	Discharged	Postpartum acquired
Sun *et al.* [36]	1	Yes	VD	37/–	6	–	No	Asymptomatic	No	–	–	Postpartum acquired
Wang *et al.* [90]	1	–	VD	38/3030	23	–	Yes	Vomiting	–	No	Discharged	Postpartum acquired
White *et al.* [53]	2	Yes	VD	39	17	–	Yes	Fever, shock, rhinorrhoea, hypoxia	Yes	No	Discharged	Postpartum acquired
		Yes	CS	39	25	–	Yes	Fever, rhinorrhoea, desaturation	Yes	No	Discharged	Postpartum acquired
Wang *et al.* [79]	1	Yes	CS	40/3205	2	17	Yes	Vomiting, deranged LFT, pneumonia	No	No	Discharged	Postpartum acquired
Yu *et al.* [41]	1	Yes	CS	39/3250	2	17	–	Respiratory distress	Yes	No	Discharged	Postpartum acquired

(continued)

Table 3. (continued)

Author	Neonates (n)	Mother COVID +	MOD	GA (weeks)/ weight (g)	NP swab positive (DOL)	NP swab negative (DOL)	Direct breast feeding	Clinical features	ICU stay	MV	Final outcome	Mode of transmission
Zamaniyan *et al.* [82]	1	Yes	CS	32/2350	1	–	No	Fever	No	No	–	Congenital (confirmed)[e]
Zeng *et al.* [42]	3	Yes	CS	40/3250	2	6	–	Lethargy, fever	Yes	No	Discharged	Postpartum acquired
				40/3360	2	6	–	Lethargy, vomiting	Yes	No	Discharged	Postpartum acquired
				31/1580	2	7	–	HMD, sepsis	Yes	Yes	Admitted	Postpartum acquired

BPD, bronchopulmonary dysplasia; CS, caesarean section; DOL, day of life; GA, gestational age; ICU, intensive care unit; MAS, meconium Aspiration syndrome; MOD, mode of delivery; NP, nasopharyngeal swab; VD, vaginal delivery.
[a]NP swab positive on Day 1 but other tests not done, so difficult to tell whether it was congenital/intrapartum or postpartum.
[b]Placenta, umbilical cord blood and breast milk positive, baby's NP swab-negative.
[c]Same NP sample negative at 37 h. Placenta-negative, SARS-CoV-2 IgG antibodies positive.
[d]NP swab taken at birth and placental swab (foetal side) positive.
[e]Amniotic fluid PCR positive.

specimens did not find any evidence to suggest vertical transmission [22, 41, 85]. However, recently published reports suggest otherwise [15, 60, 64, 82]. Lack of intrapartum transmission in this review suggests that vaginal delivery may not be a risk factor for COVID-19 transmission to the neonate and it has been supported by many studies documenting the absence of SARS-CoV-2 in vaginal secretions [37, 103]. However, the intrapartum transmission cannot be ruled out with certainty as its diagnosis requires neonate's nasopharyngeal swab testing immediately after birth (after cleaning the baby) and at 24–48 h age. However, in most reports, neonates were first tested beyond 24–48 h after birth. Also, recently SARS-CoV-2 has been documented in vaginal secretions too [64]. Overall, evidence suggests that congenital infection is possible but the incidence is extremely low and most of the cases are acquired in the postpartum period only.

Although the separation of COVID-19-positive mother from the infant might decrease the risk of postpartum transmission, it deprives the neonate of the benefits of breastfeeding. Although earlier studies advocated the safety of breast milk, detection of SARS-CoV-2 RNA from breast milk in recent studies is of concern [3, 6, 8, 19, 22, 37, 64, 67, 79, 104]. Further exploration of the safety of breast milk feeding is warranted [8, 37, 64]. As of now, considering the huge survival benefits of breast milk feeding against unknown potential threat associated with SARS-CoV-2 transmission, breast milk feeding (direct or expressed) should be given to the infants as and when the clinical condition of mother and baby permits. Mother should take adequate respiratory and hand hygiene precautions.

A number of organizations have established registries for a better understanding of COVID-19 in pregnancy and the neonatal period; however, generally their data are not available in the public domain. Data summary from the National registry for surveillance and epidemiology of perinatal COVID-19 infection (NPC-19 registry) maintained by the neonatal group of the American Academy of Pediatrics (AAP) is open to public [105]. Until 13 June 2020, there were 176 participating centres from all across the world and they enrolled 747 COVID-19-positive mothers. COVID testing was done for 624 only, of which 25 (4%) were positive. They did not provide separate data on the clinical course and outcome of COVID-positive neonates. This registry includes published and unpublished cases from various countries.

We used an extensive search strategy without any language restrictions in order to capture a global picture of COVID-19. When compared with previous reviews in which almost all the studies were from China, this review contains studies from many other countries [2, 106, 107]. Therefore, the results are likely to be representative of larger population. We included the neonatal age group only because the detailed information on clinical features, mode of transmission and outcome in this age group were lacking. To ensure uniformity, we included studies reporting RT-PCR-based diagnosis of COVID-19 only and classified cases using an explicit standard classification system [13]. This review also has

Table 4. Summary of perinatal characteristics and clinical symptoms of COVID-positive neonates (n=58)

Parameters	Number (%)
Gestational age	
Term (≥37 weeks)	29 (50)
Preterm (<37 weeks)	20 (34.4)
≥28 weeks	3 (5.2)
29–33 weeks	4 (6.9)
34–36 weeks	3 (5.2)
Exact gestation not given	10 (17.2)
Details not available	9 (15.5)
Mode of delivery	
Vaginal	18 (31)
Caesarean	29 (50)
Details not available	11 (19)
Mode of transmission	
Congenital	4 (6.9)
Postpartum acquired	41 (70.7)
Intrapartum acquired	0 (0)
Could not assigned	13 (22.4)
Clinical features	
Asymptomatic	13 (22.4)
Fever	9 (15.5)
Respiratory symptoms (respiratory distress/hypoxia/desaturation/cough, etc.)	24 (41.4)
Gastrointestinal symptoms	5 (vomiting—4 and diarrhoea—1) (8.6)
Lethargy	3 (5.2)
Poor feeding	3 (5.2)
Details not available	13 (22.4)

several limitations too. The main limitation arises from the nature of the included studies. One-third of the neonatal data is from the case reports which are expected to have high publication bias and are not suitable for inferential statistics. Also, the included case series lack internal controls and represent low-quality evidence. Furthermore, the information on indications for preterm birth and caesarean section was not reported. There is a paucity of data on mode of transmission as only a few studies tested all the required maternal and foetal samples to ascertain the mode of transmission. Although we used structured exhaustive criteria to assign the mode of transmission, but due to limited numbers, inadequate testing of required specimens and lack of standard criteria for classifying the mode of transmission, it is difficult to assign the mode of transmission with certainty. Although we followed an extensive process to exclude duplicates, the possibility of a case report later published as a part of a larger retrospective cohort cannot be ruled out with certainty.

However, given the urgency of the situation and lack of large prospective cohort studies, it would still be valuable to synthesize and critically analyse these data for future case management as well as in the planning of further studies. Also, substantial data from various registries are expected in the future which may guide us better in understanding the disease and its management.

CONCLUSIONS

The limited low-quality evidence suggests an extremely low risk of SARS-CoV-2 infections in neonates. Unlike children most of the neonates with proven SARS-CoV-2 infection were symptomatic, and a significant proportion of them required intensive care. Postpartum infection is the commonest mode of acquisition in neonates, although a few cases of congenitally acquired infection are also reported.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

Conflict of interest: All authors declare no competing interests.

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