Infants Born to Mothers With Severe Acute Respiratory Syndrome

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ABSTRACT. Severe acute respiratory syndrome (SARS) is a newly discovered infectious disease caused by a novel coronavirus. During the community outbreak in Hong Kong, 5 liveborn infants were born to pregnant women with SARS. A systematic search for perinatal transmission of the SARS-associated coronavirus, including serial reverse transcriptase-polymerase chain reaction assays, viral cultures, and paired serologic titers, failed to detect the virus in any of the infants. In addition, none of the infants developed clinical, radiologic, hematologic, or biochemical evidence suggestive of SARS. One preterm infant developed jejunal perforation and another developed necrotizing enterocolitis with ileal perforation shortly after birth. This case series is the first report to describe the clinical course of the first cohort of liveborn infants born to pregnant women with SARS. *Pediatrics* **2003;112:e254–e256. URL: http://www.pediatrics.org/cgi/content/full/112/4/e254;** ***bowel perforation, coronavirus, necrotizing enterocolitis, preterm, severe acute respiratory syndrome.***

ABBREVIATIONS. SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis; RT-PCR, reverse transcriptase-polymerase chain reaction.

The outbreak of severe acute respiratory syndrome (SARS) in Southeast Asia shocked the world.[1] In just over 3 months, this highly contagious disease affected >8400 patients in 29 countries worldwide. Hong Kong has been one of the most severely affected cities. A community outbreak in a densely populated residential complex, Amoy Gardens, and a nearby housing estate in late March affected >300 local residents and claimed >30 lives. During this outbreak, 5 liveborn infants were born to pregnant women with SARS. Cesarean section was performed in the acute phase of the disease, between 6 and 7 days of onset of fever, in 3 of the 5 pregnant women because of deteriorating maternal condition with hypotension and progressive worsening of pulmonary function (cases 1, 2, and 3). The other 2 infants were born after the mothers had fully recovered from their illnesses (cases 4 and 5). Viral studies confirmed the presence of SARS-associated coronavirus (SARS-CoV) in maternal body secretions, excreta, and/or peritoneal fluid. This case series is the first report to describe the clinical course of the first cohort of liveborn infants born to pregnant women with SARS.

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CASE REPORTS

Case 1

A male infant was born to a 34-year-old mother at 28 weeks' gestation and weighed 1035 g. Apgar scores were 5 and 9 at 1 and 5 minutes, respectively. The mother received intravenous ribavirin (400 mg, every 8 hours) and hydrocortisone (100 mg, every 6 hours) 4 days before delivery. Antenatal monitoring by cardiotocograph revealed a decreased fetal heart rate variability. The infant developed respiratory distress syndrome (RDS) necessitating positive pressure ventilation and surfactant replacement (Surventa; Abbott Laboratories, North Chicago, IL; 4 mL/kg for 2 doses, 12 hours apart), and systemic hypotension was treated with dopamine (8 μg/kg/min for 3 days). Enteral feeding was commenced on day 4. On day 8, he was treated with intravenous indomethacin (0.1 mg/kg daily for 2 doses) for a patent ductus arteriosus. The infant developed marked abdominal distension, pneumoperitoneum, and increased respiratory distress 48 hours after treatment. Intravenous ribavirin (20 mg/kg/d for 10 days) was started empirically. Laparotomy confirmed necrotizing enterocolitis (NEC) with ileal perforation measuring 0.3 cm in diameter. There were also multiple areas of necrosis at the antimesenteric border of the terminal ileum. Partial resection of the small bowel (3.5 cm) and ileostomy was performed. The infant slowly recovered from surgery but developed bronchopulmonary dysplasia. Chest radiograph revealed nonspecific diffuse haziness and ill-defined streaky densities in both lung fields. There was, however, no patchy consolidation appearance suggestive of SARS pneumonia. The infant was extubated successfully on day 25 after treatment with postnatal dexamethasone. He is now breathing in air without ventilatory support and is tolerating full enteral feeding administered via the orogastric tube. The mother died of SARS and secondary methicillin-resistant *Staphylococcus aureus* pneumonia 14 days after delivery of the infant. Reverse transcriptase-polymerase chain reaction (RT-PCR) of her nasopharyngeal aspirates was positive for SARS-CoV.

Case 2

A female infant was born to a 32-year-old mother at 26 weeks' gestation and weighed 975 g. Apgar scores were 5 and 7 at 1 and

5 minutes, respectively. The mother received intravenous ribavirin and pulsed methylprednisolone (2 g) within 72 hours of delivery. The infant had mild RDS at birth and received surfactant replacement. However, she developed gross abdominal distension and pneumoperitoneum on day 3, before enteral feeding was started. Intravenous ribavirin (10-day course) was commenced because of deteriorating respiratory function. Chest radiograph revealed diffuse atelectasis and constriction of both lung fields secondary to increased abdominal pressure. Laparotomy identified a single perforation measuring 0.5 cm at the jejunum. Bowel resection (4.3 cm) at the site of perforation and jejunostomy was performed. The rest of the bowel seemed healthy. She was weaned off mechanical respiratory support and supplemental oxygen on day 45. The infant is now taking full milk feeds via an orogastric tube. The mother was discharged from intensive care 24 days after delivery of the infant but remained oxygen dependent. RT-PCR was positive for SARS-CoV in maternal stool, cerebrospinal fluid, and peritoneal fluid specimens.

Case 3

A male infant was born to a 34-year-old mother at 32 weeks' gestation with a birth weight of 1650 g. Apgar scores were 5 and 9 at 1 and 5 minutes, respectively. The mother received intravenous ribavirin, hydrocortisone (200 mg, every 8 hours for 4 days), and pulsed methylprednisolone (500 mg/d for 3 days) before delivery. The infant did not have RDS and did not require mechanical ventilation. Fever (38.2°C) was noted on day 12, and he was treated with broad-spectrum antibiotics and a 10-day course of intravenous ribavirin. Serial chest radiographs taken after the onset of fever were consistently normal. The temperature subsided within 24 hours, and the cause was likely environmentally induced. Sepsis screening, including blood and cerebrospinal fluid cultures, was negative for bacteria, and there was no clinical, radiologic, or laboratory evidence suggestive of SARS. The infant was discharged from the hospital on day 52. His mother died of SARS 19 days after delivery. RT-PCR was positive for SARS-CoV in maternal stool samples.

Case 4

A 27-year-old mother was infected by the coronavirus at 27 weeks of pregnancy and developed mild respiratory disease. She was treated with intravenous ribavirin and hydrocortisone (100 mg every 8 hours for 5 days) during the acute phase of her illness, and her pregnancy was allowed to continue. She went into spontaneous preterm labor at 33 gestational weeks and gave birth to a female infant with a birth weight of 1395 g. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. The infant did not have RDS and had an uneventful neonatal course. This infant was not treated with ribavirin and was discharged from the hospital 5 weeks after birth. RT-PCR was positive for SARS-CoV in maternal throat and nasal swabs. There was a significant increase in maternal serology, and the acute and convalescent antibody titers for SARS-CoV were <1:25 and 1:400, respectively.

Case 5

A 30-year-old mother contracted SARS at 30 weeks of pregnancy. She developed severe respiratory failure requiring mechanical ventilation but declined preterm delivery of the infant by cesarean section in the acute phase of her illness. The mother received intravenous ribavirin, hydrocortisone (200 mg every 8 hours for 2 weeks), and 2 courses of pulsed methylprednisolone (500 mg and 3 g) for treatment of SARS. She recovered after 4 weeks of intensive treatment. Her pregnancy continued to term, and she delivered a male infant at 37 weeks' gestation with a birth weight of 1985 g. Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. The infant had an uneventful neonatal course and did not receive ribavirin. He was discharged from the hospital 3 weeks after birth. RT-PCR was positive for SARS-CoV in maternal stool specimens. There was a >4-fold increase in the maternal acute (<1:25) and convalescent antibody titer (1:1600).

A systematic search for perinatal transmission of the coronavirus was performed in all of the infants immediately after birth. SARS-CoV was not isolated or detected in any of the infants by viral isolation in cell cultures, by RT-PCR on cell culture superna-

TABLE 1. Laboratory and Radiologic Investigations of the Newborns in the First 5 Weeks of Life*

	Case 1	Case 2	Case 3	Case 4	Case 5
Virology					
RT-PCR and viral isolation					
Placental swab	Neg (×1)	Neg (×1)	Neg (×1)	Neg (×1)	Neg (×1)
Serum	Neg (×1)	—	Neg (×1)	Neg (×1)	Neg (×1)
ET aspirate	Neg (×7)	Neg (×5)	—	—	—
Pernasal/throat swab	Neg (×6)	Neg (×4)	Neg (×10)	Neg (×5)	Neg (×3)
Gastric lavage fluid	—	Neg (×1)	—	Neg (×1)	—
Urine	Neg (×5)	Neg (×3)	Neg (×8)	Neg (×7)	Neg (×5)
Rectal swab/stool	Neg (×5)	Neg (×3)	Neg (×8)	Neg (×7)	Neg (×4)
Ileostomy or jejunostomy fluid	Neg (×2)	Neg (×2)	—	—	—
Peritoneal fluid	Neg (×1)	Neg (×1)	—	—	—
CSF	—	—	Neg (×1)	—	—
Coronavirus serology (paired acute [d 1–9] and convalescent [d 21–23] titers)	<1:25/<1:25	<1:25/<1:25	<1:25/1:25	1:50/1:50	1:200/1:200
Hematology					
Lymphocyte counts ($\times 10^9$/L)	1.1–3.6	1.3–4.5	2.5–4.9	1.7–4.1	1.8
Platelet counts ($\times 10^9$/L)	118–347	107–305	238–538	308–406	317
Biochemistry					
LDH (IU/L)	284–490	279–534	288–495	484	587
CK (IU/L)	37–107	52–321	93–119	796	388
CRP (mg/L)	<3.0	<3.0	<6.0	—	—
Radiology					
Chest radiograph	Moderately severe RDS	Mild RDS	Normal	Normal	Normal
Cranial ultrasound	Normal	Normal	Normal	Normal	—
Pathology					
Histology	Ileal tissue, inflammation and erosion of mucosa; viable resection margins; no viral inclusion	Jejunal tissue, mucosal inflammation with early fibroblastic reaction; no viral inclusion	—	—	—

CK indicates creatinine kinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; ET, endotracheal; LDH, lactate dehydrogenase; Neg, negative.

* The numbers in parentheses represent the number of specimens sent to the laboratory.

tants or original samples,[2] or by acute (days 1–9) and convalescent (days 21–23) serology[3] (Table 1).

DISCUSSION

The most important question to address regarding the pregnant mother with SARS is whether the virus could be transmitted vertically to the fetus and cause clinically significant infection. Despite that all 5 mothers had pneumonia and confirmed SARS, a systematic search for the coronavirus—including serial RT-PCR assays, viral cultures, and paired serologic titers—did not demonstrate the presence of SARS-CoV in any of the newborns (Table 1). The serology for SARS-CoV in cases 4 and 5 did not show a 4-fold increase in antibody concentration, and the raised titers were likely to be associated with passive antibody transfer from mother to fetus during the late stage of pregnancy. Furthermore, their clinical pattern followed the typical clinical course of preterm infants with similar gestations. Throughout the clinical course, there were no manifestations or radiologic, hematologic, or biochemical evidence suggestive of SARS (Table 1). Our observation suggests that these newborns are not shedding the virus and have not been clinically infected. In cases 1 and 2, respiratory deterioration, after initial improvement from RDS, was associated with abdominal distension and bowel perforation. Their conditions were relieved immediately after surgical decompression and bowel resection. Although 3 infants were treated empirically with ribavirin for 10 days and tolerated the drug without major adverse effects, this treatment was probably unnecessary in retrospect. Ribavirin is a potentially potent teratogenic agent,[4] and all mothers received the drug before delivery. None of the infants was found to be dysmorphic at birth or experienced any major or minor congenital malformations. Cases 4 and 5, however, were growth retarded. Whether this was attributable to the poor maternal condition during the acute phase of illness, the use of high-dose corticosteroids or an antiviral agent, or other unknown factors remains to be determined. Nonetheless, it was unlikely that the intrauterine growth retardation was secondary to congenital SARS-CoV infection.

The severe gastrointestinal complications in 2 of the 5 infants are of concern. Other human coronaviruses have been associated with outbreaks of NEC in both preterm and term infants.[5,6] However, the negative viral studies, including peritoneal and ileostomy fluid cultures, did not support the role of coronavirus in causing NEC in case 1. The isolated upper gastrointestinal perforation in the immediate postnatal period in case 2 is also uncommon. These complications might have been coincidental but could be related to the adverse perinatal events. The mothers were severely ill with hypotension and hypoxemia, which could impair placental blood supply and oxygen delivery to the infants. The resultant intestinal ischemia in the fetus would be an important risk factor predisposing to NEC and bowel perforation.[7] Indomethacin also causes intense vasoconstriction and might further induce bowel ischemia, thereby enhancing the likelihood of perforation in case 1.[8] In addition, all mothers received systemic corticosteroids; in particular, the mother of infant in case 2 received high-dose pulsed methylprednisolone immediately before delivery. This dosage represents approximately 15 times the equivalent dose of antenatal dexamethasone (24 mg) normally used for treatment of mothers with preterm labor. Although methylprednisolone crosses the placenta less readily than dexamethasone or betamethasone, a pharmacokinetic study has shown that therapeutic levels of methylprednisolone were reaching the fetal compartment in its active form after a single intravenous injection (methylprednisolone, 125 mg) was administered antenatally.[9] Therefore, a considerable amount of methylprednisolone would have entered the fetal circulation of our infants, considering the very high maternal dose used in this series. Early (<96 hours of birth) postnatal systemic dexamethasone treatment has been associated with an increased risk of spontaneous upper gastrointestinal perforation but not NEC in very low birth weight infants.[8,10] Although the exact mechanism of bowel perforation has not been fully elucidated, it might be related to the role of prostaglandins in maintaining gastrointestinal mucosal integrity.[11] We postulate that the adverse maternal hypoxic-ischemic events, together with the use of high-dose and potent prostaglandin-modulating drugs, might have acted independently or synergistically in predisposing these vulnerable infants to the severe gastrointestinal complications. Despite that the importance of SARS-CoV in these events is not known, the supportive evidence of a causative role was not demonstrated in these infants. To our knowledge, there is no report of perinatal transmission of other human coronaviruses in the literature.

CONCLUSIONS

Our observations suggest that the first 5 newborns of mothers with SARS did not develop SARS. Abdominal signs and symptoms should be monitored carefully in these infants for severe gastrointestinal pathologies after birth.

REFERENCES

1. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986–1994
2. Bellini WJ. SARS-CoV specific RT-PCR primer. Available at: http://www.who.int/csr/sars/CDCprimers.pdf
3. Severe acute respiratory syndrome (SARS): laboratory diagnostic tests. Available at: http://www.who.int/csr/sars/diagnostictests/en/
4. Ferm VH, Willhite C, Kilham L, et al. Teratogenic effects of ribavirin on hamster and rat embryos. *Teratology*. 1978;17:93–101
5. Chany C, Moscovici O, Lebon P, Rousset S. Association of coronavirus infection with neonatal necrotizing enterocolitis. *Pediatrics*. 1982;69:209–214
6. Resta S, Luby JP, Rosenfeld CR, Siegel JD. Isolation and propagation of a human enteric coronavirus. *Science*. 1985;229:978–981
7. Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. *N Engl J Med*. 1984;310:1093–1103
8. Stark AR, Waldemar AC, Tyson JE, et al. Adverse effects of early dexamethasone treatment in extremely low birth weight infants. *N Engl J Med*. 2001;344:95–101
9. Anderson GG, Rotchell Y, Kaiser DG. Placental transfer of methylprednisolone following maternal intravenous administration. *Am J Obstet Gynecol*. 1981;140:699–701
10. Halliday HL, Ehrenkranz RA, Doyle LW. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;(1):CD001146
11. Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill; 1996:622

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