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Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome

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Objective: This study was undertaken to evaluate the pregnancy and perinatal outcomes of pregnant women with severe acute respiratory syndrome (SARS).

Study design: All pregnant women (12) who presented with SARS in Hong Kong between February 1 and July 31, 2003, were included. The pregnancy and perinatal outcomes were collected. Evidence of perinatal transmission of virus was assessed with the SARS-associated coronavirus reverse-transcriptase polymerase chain reaction on cord blood, placenta tissue, and subsequent follow-up of the neonate on serology.

Results: Three deaths occurred among the 12 patients, giving a case fatality rate of 25%. Four of the 7 patients (57%) who presented in the first trimester had spontaneous miscarriage. Four of the 5 patients who presented after 24 weeks were delivered preterm. Two mothers recovered without delivery, but their ongoing pregnancies were complicated by intrauterine growth restriction. No newborn infant had clinical SARS and all investigations were negative for SARS.

Conclusion: SARS during pregnancy is associated with high incidences of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction. There is no evidence of perinatal SARS infection among infants born to these mothers.

This is a multicenter observational study and the data were collected from 5 public hospitals in Hong Kong. The following hospitals are involved: Prince of Wales Hospital, Princess Margaret Hospital, Queen Elizabeth Hospital, Tuen Mun Hospital, and United Christian Hospital.

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Since November 2002, severe acute respiratory syndrome (SARS) has affected 8437 persons and has caused more than 800 deaths worldwide.[1] SARS is a new disease caused by a novel coronavirus[2,3] that causes atypical pneumonia, which may progress to respiratory failure.[4] It appeared that the SARS outbreak was currently under controlled, though the problem may re-emerge during the winter. There is no published information on the outcomes of pregnant women infected with SARS. Given the significant maternal and perinatal morbidity and mortality of most viral pneumonia in pregnancy, SARS may impose greater risk in pregnant compared to nonpregnant individuals. We reported the pregnancy and perinatal outcomes of all pregnant women affected during the outbreak in Hong Kong.

Material and methods

Between February 1 and July 31, 2003, all pregnant women in Hong Kong whose disease met the World Health Organization (WHO) case definition of May 1, 2003, of SARS were included.[5] These patients were jointly managed by the infectious disease specialists, intensive care physicians, respiratory physicians, obstetricians, and midwives. The (medical) clinical course and demographic data were abstracted from the records.

Pregnancies in the first trimester were identified by pregnancy tests offered to all female SARS patients suspected to be pregnant. Ultrasound examination was performed as soon after admission as practical. All pregnant women at more than 24 weeks of gestation, once classified as probable cases of SARS, were transferred to Princess Margaret Hospital, which is a designated hospital for infection control in Hong Kong, for further management. Medical treatment was offered to the patients while maternal and fetal conditions were closely monitored. Indications for early delivery included maternal deterioration, failure to maintain adequate oxygenation or difficulty with mechanical ventilation because of the gravid uterus, fetal compromise or other obstetric indications. Daily cardiotocography (CTG) was performed for pregnancies after 28 weeks of gestation. Fetal growth was assessed by serial ultrasound scans every 2 weeks. Liquor volume measurement and umbilical Doppler artery blood flow studies were performed on a weekly basis.

The obstetric and neonatal outcomes were collected. Major medical complications were identified. Evidence of perinatal transmission of virus was assessed by the SARS-associated coronavirus reverse-transcriptase polymerase chain reaction (SARS-CoV RT-PCR) and viral culture on cord blood, placenta tissue, and amniotic fluid at or after delivery as appropriate. Maternal blood was removed before the cord blood was collected with a sterile syringe. A 1-cm cubic of fresh placenta tissue was removed after it had been thoroughly rinsed with sterile saline solution and dissected from the chorionic plate. The remaining placenta tissue was sent for histopathology and/or electron microscopy, particularly searching for viral inclusion bodies or particles. The newborn infants were followed-up with SARS-CoV antibody titers for evidence of SARS infection.

Qualitative RT-PCR and SARS-CoV antibody testing

The samples collected were sent to the Public Health Laboratory, Government Virology Unit of Hong Kong for qualitative SARS-CoV PCR testing. The technique was described in a recent Center for Disease Control publication.[6] For SARS-CoV antibody titer, enzyme-linked immunosorbant assay test was used, a test detecting a mixture of immunoglobulin M and immunoglobulinG antibodies in the serum of SARS patients yields positive results reliably at around day 21 after the onset of illness.[7]

Results

During the study period, there were a total of 12 Southern Chinese patients with SARS admitted to 5 public hospitals in Hong Kong (Table I). The maternal age ranged between 27 to 44 years. There were 5 health care workers and 7 others who acquired the disease in the community. Seven women were less than 13 weeks of gestation (3-12 weeks) and the other 5 patients were in their late second and third trimesters at presentation. None of the patients had underlying medical disease.

All patients had high fevers (>38°C) and most presented with chill, rigors, malaise, and myalgia. Only 33% of the pregnant patients presented with shortness of breath. Physical examination of the chest revealed crackles with or without percussion dullness. Lymphopenia ($<1.0\times10^9$/L) was observed in 8 patients at presentation, but subsequently all had lymphopenia develop. Some patients had mildly elevated lactate dehydrogenase (5/12) and aminotransferase (4/12) levels. Serial chest radiographs showed progressive air-space disease in all patients, similar to those reported earlier in nonpregnant patients.[6] There was no evidence of infection by *Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila*. Viral serology for adenovirus, influenza A and B, parainfluenza type 1 to 3, and respiratory syncytial virus were negative. All patients had either positive SARS-CoV RT-PCRs or raised SARS-CoV antibody titers (>100). Patient 7 was retrospectively diagnosed to have SARS. She is a health care worker and had cared for a patient with atypical pneumonia from Guangdong Province, China, before the SARS outbreak in Hong Kong. She subsequently had a high fever and atypical pneumonia develop 5 days later.

All patients were given broad-spectrum antibiotics, namely, beta-lactams and macrolides or fluoro-quinolones.

Table I Maternal characteristics, clinical presentation, and treatment received

	1	2	3	4	5	6	7	8	9	10	11	12	
Case	First trimester							>24 wks of gestation					Proportion (%)
Age	33	34	44	24	24	25	26	27	30	32	34	34	NA
Gravidity	2	2	4	1	1	3	2	2	1	3	2	2	NA
Parity	1	1	3	0	0	0	0	1	0	0	1	1	NA
Health care worker	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No	5/12 (42)
Gestastional age at diagnosis (wks)	4	4	5	3	6	12	3	28	30	26	32	27	NA
Other family members affected	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	3/12 (25)
Symptoms													
Myalgia	+	+	+	+	+	+	+	+	+	+	+	+	12/12 (100)
Malaise	+	+	+	−	+	+	+	+	+	+	+	+	11/12 (92)
Chills and rigors	+	+	+	+	+	+	+	+	+	+	+	−	11/12 (92)
Cough	+	−	+	+	−	+	+	+	+	−	+	+	9/12 (75)
Headache	+	+	+	−	+	−	−	−	−	+	−	+	6/12 (50)
Shortness of breath	−	−	+	−	−	+	−	+	−	−	−	+	4/12 (33)
Runny nose	+	−	−	−	−	−	−	−	+	−	−	+	3/12 (25)
Sore throat	−	−	−	−	−	−	−	−	+	−	−	+	2/12 (17)
Diarrhea	−	−	−	+	−	−	−	−	−	+	−	−	2/12 (17)
Chest pain	−	−	−	−	−	−	−	+	−	−	−	−	1/12 (8)
Onset to presentation (d)	2	3	5	3	1	1	3	2	3	2	7	5	NA
Investigations													
Lymphopenia	−	−	+	−	+	+	+	+	+	−	+	+	8/12 (67)
Leukocytosis	−	−	−	−	+	−	+	+	−	+	−	−	4/12 (33)
Thrombocytopenia	−	−	+	−	+	+	+	−	−	−	−	+	4/12 (33)
Confirmation SARS-CoV RT-PCR	−	+	+	−	−	+	NA	+	+	+	+	+	8/11 (73)
SARS-CoV antibody titre >100	+	−	NA	+	+	NA	+	+	+	+	NA	NA	7/8 (88)
CXR or CT evidence of pneumonia	+	+	+	+	+	+	+	+	+	+	+	+	12/12 (100)
Treatment													
Antibiotics	+	+	+	+	+	+	+	+	+	+	+	+	12/12 (100)
Ribavirin	+	+	+	+	+	+	−	+	+	+	+	+	11/12 (92)
IV hydrocortisone	+	−	+	+	+	+	−	+	+	+	+	+	10/12 (83)
Methyl-prednisolone	−	+	+	+	+	+	−	−	+	+	+	+	9/12 (75)
Oral prednisolone	+	−	+	+	+	+	−	+	+	+	+	+	10/12 (83)

NA, Not applicable; *SOB*, shortness of breath; *CXR*, chest X-ray; *CT*, computed tomograph; *IV*, intravenous.

All patients, except patient 7, were given ribavirin and/or hydrocortisone after 48 hours of observation. All couples were fully informed of the potential teratogenic effect of ribavirin and all opted to receive this treatment. Ten patients also had 1 or more courses of pulse methyl-prednisolone as described in previous publications.[8] The fever lasted between 2 and 9 days. Five patients had high fevers develop again after initial response. Six patients (50%) were admitted to the intensive care unit (ICU) because of decreased blood oxygen saturation. The length of stay ranged from 14 to 37 days. Four patients (33%) required mechanical ventilation ranging from 16 to 37 days. After ribavirin therapy all patients became anemic (Hb <10g/dL).

The major medical complications among these patients included disseminated intravascular coagulopathy (patients 3, 8, and 12), renal failure (patients 3, 9, and 12), secondary bacterial pneumonia (patients 3 and 12), sepsis (patients 11 and 12), adult respiratory distress syndrome (patients 3, 10, 11, and 12), cardiovascular collapse (patient 11), abdominal wound dehiscence (patients 11 and 12), and surgical emphysema (patient 12). Three deaths occurred of which 2 patients (patients 3 and 11) died of progressive respiratory failure and 1 patient (patient 12) died of methicillin-resistant *Staphylococcus aureus* pneumonia associated with cardiovascular collapse not responsive to active resuscitation.

Six of the 7 women (except patient 7) presenting in the first trimester had positive pregnancy tests during hospital admission. Five women (patients 2-6) had ultrasound confirmation of an intrauterine gestational sac. In these, absence of fetal pole was noted in 3 women (patients 2, 3, and 4) and a single fetal pole with fetal heart pulsation was detected in 2 (patients 5 and 6). Ultrasound failed to demonstrate an intrauterine sac in 1 woman (patient 1) and she did not have any sign or symptom of ectopic pregnancy or spontaneous miscarriage. Serial serum human chorionic gonadotrophins rapidly decreased and she was considered to have a very early pregnancy loss.

Four of the 7 patients presented in first trimester had spontaneous miscarriages between 2 to 5 weeks after the onset of illness (Table II). Patient 7 did not receive ribavirin or steroid and has an uncomplicated ongoing pregnancy. Patients 5 and 6 had termination of pregnancies at 10 weeks and 15 weeks of gestation for social reasons after they had recovered from SARS. Gestation at presentation for the other 5 patients ranged from 26 to 32 weeks. Four pregnancies (80%) resulted in preterm delivery. Three patients were delivered by emergency cesarean section between 26 and 32 weeks of gestation because of maternal deterioration, secondary to failure to maintain adequate blood oxygen saturation, despite on 100% oxygen (patients 10 to 12). Patient 10 also had fetal distress develop before cesarean section. After delivery, the need for supplemental oxygen was reduced in all mothers. One patient was extubated 20 hours after delivery, but she was reintubated 32 hours later for oxygen desaturation again. The ventilator settings for the other 2 patients were unchanged after delivery.

Two pregnancies (patients 8 and 9) that did not require early intervention had intrauterine growth restriction (IUGR) develop during treatment. Both pregnancies were also complicated by oligohydramnios. Fetal surveillance with antenatal CTG and umbilical arterial Doppler velocimetry was satisfactory. Patient 8 had spontaneous preterm labor at 33 weeks of gestation during the convalescence period, which did not respond to tocolysis. Patient 9 had emergency lower-segment cesarean section for intrapartum nonreassuring CTG.

There was no clinical or serologic evidence suggestive of vertical transmission of the coronavirus (Table III). To date, none of the 5 newborn infants show any evidence of perinatal SARS infection. In particular, the first 3 newborn infants (newborn infants 3-5) were delivered during the acute stage of maternal SARS infection and were exposed to a significant risk of perinatal infection. Peritoneal fluid (patient 10) and samples of body fluid were positive for SARS-CoV at the time of cesarean section. The SARS-CoV RT-PCRs and viral cultures from nasal swab, blood, urine, and stool were all negative in these infants. There was also no significant rise in paired acute and convalescent SARS-CoV antibody titers.

Three newborn infants delivered soon after the mothers presented with SARS were average in size, whereas the other 2 were growth restricted with birth weight below the fifth percentile for gestation. Of the newborn infants delivered preterm, 2 had serious complications develop related to prematurity (Table III).

RT-PCRs and viral cultures of the cord blood and placenta tissues were all negative for SARS-CoV. Amniotic fluid obtained from patients 5, 6, and 9 were also negative for SARS-CoV. No viral inclusion body or particle was detected in the products of conceptions. The placental findings from the 5 deliveries are summarized in Table III. All the placentae showed trimmed weight falling short of the fifth percentile for gestation, with a weight deficiency of 8% to 47%. Three placentae (patients 10 to 12) had normal histopathologic findings. Two placentae from pregnancies (patients 8 and 9) complicated by IUGR showed avascular fibrotic terminal villi with thrombotic vasculopathy in some stem villi. In addition, placental infarction was evident grossly and on histology in the placenta of patient 9. The percentage of infarcted placental tissue was estimated to be about 10%. No placentae showed chorioamnionitis, funisitis, villitis, viral inclusion, or other features of infection. No significant erythroblastosis was noted.

Comment

The risk of viral pneumonia is significantly higher among pregnant women compared with the general population, especially when there is no effective antiviral therapy.[9] The influenza epidemic of 1918 and Asian flu epidemic of 1957 had a maternal mortality rate of 30% to 50%.[10,11] SARS has the same impact, and pregnant women appear to have a worse clinical course with a case fatality rate of 25%. In the current series, more patients required ICU admissions (50%) and mechanical ventilation (33%) compared with the nonpregnant adult population (20% ICU admission).[8] This poor outcome could be ascribed to the physiologic changes in pulmonary function during late pregnancy. The gravid uterus has been shown to elevate the diaphragm by up to 4 cm in the third trimester, while oxygen consumption is increased by 20% in pregnancy and functional residual capacity is decreased, rendering the woman intolerant to hypoxia.[12]

Fifty-seven percent of our patients had spontaneous miscarriage, which was higher than the 15% to 20% widely reported early pregnancy loss rate.[13] The increased miscarriage risk was unlikely to be due to transplacental infection, as there was an absence of viral particles in the products of conceptions. Severe maternal respiratory failure and hypoxemia may disrupt uterine placental flow and cause miscarriage. Ribavirin is a commonly used first-line medication for the management of SARS in Hong Kong. Six patients had ribavirin, and a significant embryocidal effect has been observed in rabbits and mice, it may be possible that during this anembryonic stage ribavarin was the cause of spontaneous miscarriage.[14,15] There are no human data for early pregnancy use and such postulation needs further confirmation. Ribavirin was also associated with significant teratogenic effects in animal studies.[14,16] Patients who decide to use ribavirin in early pregnancy should be given the option for termination of pregnancy.

In maternal pneumonia, neonatal morbidity frequently arises as a result of preterm labor (15%-44%).[17,18] Eighty percent of our cohort who presented

Table II Maternal complications and pregnancy outcomes

Case	1	2	3	4	5	6	7	8	9	10	11	12	
Maternal outcome													
ICU admission	−	−	+	+	−	−	−	−	+	+	+	+	6/12 (50)
Mechanical ventilation	−	−	+	−	−	−	−	−	−	+	+	+	4/12 (33)
Death	−	−	+	−	−	−	−	−	−	−	+	+	3/12 (25)
Spontaneous miscarriage	+	+	+	+	−	−	−	NA	NA	NA	NA	NA	4/7 (57)
Preterm delivery	NA	NA	NA	NA	NA	NA	NA	+	−	+	+	+	4/5 (80)
Spontaneous preterm labor	NA	NA	NA	NA	NA	NA	NA	+	−	−	−	−	1/5 (20)
Tocolysis	NA	NA	NA	NA	NA	NA	NA	+	−	−	−	−	1/5 (20)
IUGR	NA	NA	NA	NA	NA	NA	NA	+	+	NA	NA	NA	2/5 (40)
Cesarean section	NA	NA	NA	NA	NA	NA	NA	−	+	+	+	+	4/5 (80)
PPH	NA	NA	NA	NA	NA	NA	NA	−	−	−	−	−	0/5 (0)

PPH, Postpartum hemorrhage.

Table III Neonatal outcome and placental findings

Newborn infant	1	2	3	4	5
Mother's case no.	8	9	10	11	12
(I) Neonatal outcome					
Gestation at delivery (wks)	33	37	26	32	28
Preterm labor	Yes	No	No	No	No
BW (g)	1395	1985	975	1650	1035
SGA/AGA/LGA	SGA	SGA	AGA	AGA	AGA
Fetal distress	No	Yes	No	No	Yes
CXR	Normal	Normal	RDS	Normal	RDS
Clinical SARS	No	No	No	No	No
SARS-CoV RT-PCRs	Negative	Negative	Negative	Negative	Negative
Rise in SARS-CoV antibody titre	No	No	No	No	No
Complications	No	No	RDS, bowel perforation	No	RDS, NEC PDA
(II) Placental findings					
Trimmed weight (g)	170	240	220	250	190
Fifth percentile weight for gestation (g)	320	360	240	300	260
Weight difference from fifth percentile (2 minus 1) (g)	150	120	20	50	70
Percentage weight deficient (3/2 × 100)	47%	33%	8%	17%	27%
Pathology	Avascular villi	Avascular villi, placental infarct	Normal	Normal	Normal
Duration from diagnosis of SARS to delivery (wks)	5	7	0	0	1

BW, Birth weight; *SGA*, small for gestational age; *AGA*, average for gestational age; *LGA*, large for gestational age; *RDS*, respiratory distress syndrome; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus.

after 24 weeks were delivered preterm and therefore were associated with higher neonatal morbidity. Other fetal/neonatal complications include IUGR, intrauterine demise, and neonatal death.[17,18] IUGR appears to be a common sequel among our patients who carried on with their pregnancies. This might be due to the severe maternal respiratory illness affecting the oxygen supply to the fetuses. These patients had frequent episodes of oxygen desaturation, often falling below 90%. The situation resembles that of those living at high altitudes, causing a low arterial partial pressure of oxygen[19,20] and consequent IUGR. The general impact of a severe maternal debilitating illness on fetal growth also needs to be considered. The placental findings of placental infarction (patient 9) indicate maternal thrombosis, and the avascular villi (patients 8 and 9) suggest fetal thrombosis. There was also significant placental weight reduction relating to the duration of SARS before delivery (Table III). Again, these changes were likely to represent complications of the hypoxemia and circulatory insufficiency in both the mother and fetus as a result of SARS. The observed fetal growth restriction is unlikely to be due to hydrocortisone or methyl-prednisolone, as neither steroid crosses the placenta readily.

The risk of perinatal transmission of SARS-CoV was low, as there was no evidence of the presence of virus/viral particles in the products of conception or the infants. Direct contact with maternal body fluid that contained SARS-CoV put the infants at high risk of perinatal infection. Preventive measures at delivery, such as performing nasopharyngeal suction before first breath and cleansing the infant soon after birth, might help to reduce the viral load. It was a fortunate finding from our cohort that there was no evidence of vertical transmission, despite close contact with SARS virus. Indeed, there should be a theoretical advantage of delaying delivery in these patients to avoid the exposure of these infants to the virus at birth. The passage of maternal SARS-CoV antibodies across the placenta to the fetal circulation should have additional protective effect on the fetus/neonate. Nevertheless, it was our experience that the timing of delivery was frequently dictated by the deteriorating maternal condition.

This observational study consisted of only 12 pregnant women and the number of patients involved is small. We caution the readers to take this into account when interpreting the results and conclusion drawn from the study, as some of the above observations may be due to chance occurrence. As there is currently no large series on pregnant women with SARS, we believed such information is useful in guiding us in our future management of such women.

In conclusion, our experience showed that SARS during pregnancy is associated with high maternal morbidity and mortality. There were high incidences of spontaneous miscarriage, preterm delivery, and IUGR. There appeared to be a low risk of clinical SARS among infants of SARS patients, even when the delivery occurred during acute maternal infection. The adverse pregnancy outcomes might be due to the effects of SARS infection on pregnancy as well as to the medical treatment received for SARS.

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