

A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome

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Objective To compare the clinical courses and outcomes of pregnant severe acute respiratory syndrome (SARS) patients and non-pregnant SARS patients.

Design A case–control study.

Setting Tertiary Hospital for Infectious Disease.

Sample Ten pregnant and 40 non-pregnant female patients infected with SARS.

Methods Clinical course and outcomes of pregnant SARS patients were compared with a group of non-pregnant SARS patient. Cases and controls were matched with respect to sex, age, timing of contracting SARS, health care workers status and underlying illness.

Main outcome measures The incidence of intensive care unit admission, intubation, medical complications and death rate.

Results Pregnancy had no discernible impact on clinical symptoms and presentation delay. Four out of the 10 pregnant patients, nevertheless, required endotracheal intubation and six were admitted to the intensive care unit (ICU), as compared with 12.5% intubation rate ($P = 0.065$) and 17.5% ICU admission rate ($P = 0.012$) in the non-pregnant group. More pregnant SARS patients developed renal failure ($P = 0.006$) and disseminated intravascular coagulopathy ($P = 0.006$), as compared with non-pregnant SARS group. There were three deaths in the pregnant group, whereas there was no death in the non-pregnant control group ($P = 0.006$).

Conclusion Pregnant women with SARS experience a worse clinical course and poorer outcomes compared with non-pregnant women.

INTRODUCTION

Severe acute respiratory syndrome (SARS) has caused a worldwide epidemic since November 2002. The disease is caused by a novel coronavirus^{1,2} and has infected more than 8000 people, claiming over 750 lives as of September 2003.³ Affected patients have symptoms of atypical pneumonia and may progress to severe respiratory failure.^{3,4} There is legitimate concern, however, that pregnant women might have a different disease course and outcome,⁵ given the physiological changes in respiratory and immunological systems.

We herein reported the largest case–control study to compare the clinical course and outcomes of severe acute respiratory syndrome among pregnant SARS women with non-pregnant SARS patients.

METHODS

During the SARS outbreak in Hong Kong between 15 February 2003 and 31 May 2003, there were 1755 cases and 299 deaths. Inclusion criteria included cases fulfilling the modified case definition by World Health Organisation.^{3,6} We only included cases with either positive SARS associated coronavirus polymerase chain reaction or raised SARS-CoV antibodies (>100 titres).

Twelve pregnant women were infected, and two were excluded because they were not matched. One pregnant woman was admitted with atypical pneumonia before the SARS outbreak and was treated as viral pneumonia. She was retrospectively diagnosed having SARS after her serum SARS associated coronavirus (SARS-CoV) antibody was raised (>300 titres). The other pregnant woman was admitted with fever for investigation; her initial investigations did not support SARS infection. She did not have any

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Table 1. Symptoms and clinical features of two study cohorts. Values are presented as mean [SD] or *n* (%).

	Pregnant SARS patients (<i>n</i> = 10)	Non-pregnant SARS patients (<i>n</i> = 40)	<i>P</i>
Age (years)	31.6 [5.9]	31.5 [5.5]	0.97
Fever	10 (100)	40 (100)	
Chills and rigors	9 (90)	25 (63)	0.14
Headache	6 (60)	17 (43)	0.48
Malaise	9 (90)	29 (73)	0.42
Diarrhoea	1 (10)	9 (23)	0.66
Cough	7 (70)	14 (35)	0.73
Breathlessness	3 (30)	9 (23)	0.69
Myalgia	10 (100)	29 (73)	0.09
Chest pain	1 (10)	4 (10)	1.00
Sore throat	2 (20)	5 (13)	0.63
Duration of symptoms before admission (days)	3.3 [1.8]	4.1 [2.0]	0.26

fever after admission but developed fever one week later. She was suspected to have contracted SARS within the ward and was confirmed on reverse transcriptase–polymerase chain reaction. Because of her unique presentation, we could not find appropriate control for matching. Clinical findings and laboratory data of the remaining 10 pregnant patients were prospectively documented, and compared with another historical cohort of matched SARS non-pregnant patients over the same study period. Each of the pregnant patients was matched with four non-pregnant patients. They were matched with respect to sex, age, timing of contacting SARS, health care workers status, underlying illness and residence in the Amoy Garden high-rise housing estate, where there was a community outbreak with over 300 residents infected.⁷ The death rate for health care workers was considerably lower than the general population and was higher among Amoy Garden's residents.⁸ The first four consecutive patients, fulfilling the matching criteria and admitted after the index pregnant patients, were chosen as the control group.

Analyses of the clinical course and outcomes were performed by Statistical Package for the Social Sciences for Windows software, version 11.0 (SPSS, Chicago, Illinois). The data were expressed in mean (SD) unless

otherwise specified. Univariate comparisons between the pregnancy group and non-pregnant group were made with the use of Student's *t* test for continuous variables and with the χ^2 test or Fisher's exact test for discrete variables. *P* values of less than 0.05 were taken as statistical significance, and all probabilities were two-tailed.

RESULTS

The mean age in the pregnant group was 31.6 and in the non-pregnant group was 31.5. Forty percent of the women were health care workers and the rest were from Amoy Garden. Among the 10 pregnant patients, five were in the first trimester and the other five were in late second and third trimester (26–32 weeks). None of the patients have underlying medical diseases. Four of the five patients presented in first trimester had spontaneous miscarriage. Four of those presented after second trimester had preterm delivery (26–33 weeks). None of the five newborns had SARS but three had complications related to prematurity.

The symptoms and investigation results of the two groups were compared in Tables 1 and 2, respectively. Pregnancy had no discernible impact on the presentation pattern of SARS. Fever was the universal presenting symptom, and lymphopenia (absolute lymphocyte count <1000/mm³) was noted in all pregnant patients during the course of the SARS illness. There was no statistical difference in the temperature and lymphocyte count on admission between the two groups. The clinical manifestation in the two groups closely resembled those in previously reported series.^{4,9–11} The time between symptom onset and admission was not different statistically. Features of atypical pneumonia were evident on chest X-rays or high-resolution computed tomography. Baseline haemoglobin level on admission was lower for the pregnant group than that of the non-pregnant group (11.5 g/dL vs 12.7 g/dL, *P* = 0.036). However, treatment regimens were similar in the two groups. All women were treated with broad-spectrum antibiotics. If there was no response within 48 hours, ribavirin and steroid were instituted. There was no difference in the timing of instituting antibiotic, ribavirin or steroid therapies. There were decreases in haemoglobin level in

Table 2. Laboratory results and imaging results of two study cohorts. Values are presented as mean [SD] or *n* (%).

	Pregnant SARS patients (<i>n</i> = 10)	Non-pregnant SARS patients (<i>n</i> = 40)	<i>P</i>
Admission haemoglobin (g/dL)	11.5 [1.2]	12.7 [1.4]	0.04
Lowest haemoglobin (g/dL)	8.4 [1.8]	10.6 [1.5]	<0.0001
Drop in haemoglobin (g/dL)	3.2 [1.7]	2.1 [1.5]	0.06
Lymphopenia	10 (100)	40 (100)	
Leukocytosis	10 (100)	40 (100)	
Thrombocytopenia	3 (30)	17 (43)	0.72
Mean admission lactate dehydrogenase (U/L)	408.3	207.4	<0.0001

Lymphopenia was defined as absolute lymphocyte count below 1000/mm³, and thrombocytopenia as platelet count less than 140,000/mm³.

Table 3. Univariate analyses of the complications and outcomes between pregnant and non-pregnant SARS patients. Values are expressed as mean [SD] or *n* (%), unless otherwise indicated.

	Pregnant SARS patients (<i>n</i> = 10)	Non-pregnant SARS patients (<i>n</i> = 40)	Odd ratios	95% CI	<i>P</i>
Hospital stay (days)	27.0 [12.6]	17.3 [5.5]			0.01
Renal failure	3 (30)	0 (0)	NA	NA	0.01
Sepsis	2 (20)	0 (0)	NA	NA	0.04
DIC	2 (20)	0 (0)	NA	NA	0.04
ICU admission	6 (60)	7 (18)	7.07	1.57–31.86	0.01
Mechanical ventilation	4 (40)	5 (13)	4.67	0.97–22.53	0.07
Death	3 (30)	0 (0)	NA	NA	0.01

DIC = disseminated intravascular coagulopathy; ICU = intensive care unit; NA = not applicable because of zero event rate.

both groups; 47% of non-pregnant women and 60% of pregnant women experienced haemoglobin level decrement of more than 2 g/dL. The nadir haemoglobin level was 8.4 g/dL in the pregnant group which was significantly lower than that in the non-pregnant group (10.6 g/dL). There was a trend of a more obvious fall in haemoglobin level in the pregnant group (3.2 g/dL vs 2.1 g/dL, $P = 0.055$). There was no difference in the nadir lymphocyte counts and platelet counts. Besides, the lactate dehydrogenase level (normal range 87 to 213 U/L) in the disease course was higher in the pregnant group (408.3 U/L vs 207.4 U/L, $P < 0.0001$).

Table 3 showed the serious complication rates, requirement of endotracheal intubation and intensive care, and clinical outcomes between two groups of patients. In particular, significantly more pregnant women had complications of acute renal failure, sepsis and disseminated intravascular coagulopathy. In the pregnant group, significantly more patients required intensive care (60% vs 17.5%, $P = 0.012$). Forty percent of patients in the pregnant group needed mechanical ventilatory support with positive end-expiratory pressure, whereas only 12.5% in the non-pregnant women required mechanical ventilation. However, this difference did not reach statistical significance. There were three deaths in the pregnant group, whereas all women in the non-pregnant group survived ($P = 0.006$). After excluding the fatal cases, the pregnant women required a longer hospital stay than the non-pregnant group (27.0 days vs 17.3 days, $P = 0.005$).

DISCUSSION

We reported an analysis of clinical outcomes in 10 pregnant SARS patients—the largest cohort that has been studied to date. We documented a notable increase in mortality and morbidity in SARS pregnant patients. This is not unexpected, given the previous observations that the risk of viral pneumonia is significantly higher among pregnant women compared with the general population.¹² Indeed, the maternal mortality was 30–50% in the influenza epidemic in 1918.¹³ Furthermore, the mortality rate in pregnant women was twice that in non-pregnant women in the Asian-flu epidemic in the 1950s.¹⁴ Besides, pneumonia was reported to be

a more common complication of varicella infection in pregnant women compared with the general population.¹⁵

The worse outcome can be partly explained by the physiological changes in immunity and respiratory mechanics in pregnancy. Diminished cell-mediated immunity has been documented in pregnant women.^{16,17} Maternal lymphocytes obtained during the second and third trimesters exhibit a decreased proliferative response to antigen stimuli. There is also a decrease in natural killer cell activity. Given the presence of relative immunosuppressive status of pregnancy, it could set the stage for uncontrolled replication of the coronavirus.

The observation of increased morbidity and mortality risks with pregnant SARS patients, conversely, is in accordance with the gestational change of pulmonary physiology. Notably, two out of three deaths occurred in patients in the second and third trimesters, during which gravida uterus could elevate the diaphragm by up to 4 cm.¹⁸ There is also a decrease in both expiratory volume and residual volume, resulting in a 9.5% to 25% drop in functional residual capacity. Total lung capacity also decreased towards term. Moreover, there is a 20% increase in oxygen demand in pregnancy.¹⁸ Indeed, three patients in the third trimester required delivery for deteriorating maternal hypoxaemia. Initial improvement in ventilation setting was observed. However, two of them succumbed finally.

There is great debate as to the optimal pharmacotherapy of SARS. Ribavirin has been the main drug used in Hong Kong, although clinical trials are lacking.¹⁹ The drug has been shown to cause teratogenic effects in animals.^{20,21} Little information was known about its effect in human pregnancy. Putatively, the poor outcome could be due to a delay in starting the medication, especially in the first trimester. However, such a delay was not observed in our pregnant cohort.

Ribavirin was well known to cause haemolytic anaemia when used for treatment for hepatitis C infection.²² We found half of our patients had a haemoglobin drop of more than 2 g/dL. This was comparable with previous reports by various groups in Hong Kong²³ and Canada.²⁴ Physiological haemodilution in pregnancy lowers the haemoglobin level of pregnant women, as reflected in the difference of initial haemoglobin level between the two groups. A

further drop in haemoglobin level might jeopardise the stressed oxygen carrying capacity of mother, adding further risk to pregnant SARS patients. In fact, the haemoglobin at presentation and the lowest haemoglobin were significantly lower in the pregnant group. The pregnant women also tended to have a more substantial drop, albeit insignificant statistically, in the haemoglobin level. We cannot rule out the possibility of increased susceptibility to haemolysis adverse effect among pregnant patients.

Finally, a higher level of lactate dehydrogenase at presentation had been associated with poor outcome among SARS patients in most,^{8,24,25} but not all, case series.^{26,27} Likewise, a higher lactate dehydrogenase level was found in our pregnant group, reflecting tissue necrosis related to immune hyperactivity in SARS. The presence of such adverse outcome predictor may reflect the severity of the disease course in pregnancy.

In summary, we have demonstrated worse clinical outcomes among pregnant patients with SARS. The findings from our investigation provide insight into the impact of pregnancy on the morbidity and mortality associated with SARS. We should remain vigilant in our surveillance activities, in particular, among the pregnant population. Whether pregnant patients with SARS warrant new treatment strategy remains to be established.

References

1. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;**348**:1953–1966.
2. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003;**361**:1319–1325.
3. World Health Organization. Severe Acute Respiratory Syndrome (SARS). Available: <http://www.who.int/csr/sars/> (Accessed 25 September 2003).
4. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;**348**:1977–1985.
5. Wong SF, Chow KM, de Swiet M. Severe acute respiratory syndrome and pregnancy. *Br J Obstet Gynaecol* 2003;**110**:641–642.
6. WHO. Severe acute respiratory syndrome (SARS). *Wkly Epidemiol Rec* 2003;**78**:81–83.
7. Cheng VC, Peiris JS, Yuen KY. SARS bulletin from Hong Kong: what might we have done better? *Clin Infect Dis* 2003;**36**:iii.
8. Chim SS, Tsui SK, Chan KC, et al. Genomic characterisation of the severe acute respiratory syndrome coronavirus of Amoy Gardens outbreak in Hong Kong. *Lancet* 2003;**362**(9398):1807–1808 (November 29).
9. 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.
10. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;**361**:1767–1772.
11. Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome. *N Engl J Med* 2003;**349**:2431–2441.
12. Ramsey PS, Ramin KD. Pneumonia in pregnancy. *Obstet Gynecol Clin North Am* 2001;**28**:553–569.
13. Harris JM. Influenza occurring in pregnant women. *JAMA* 1919;**72**:978–983.
14. Greenberg M, Jacobzine H, Paketer J, Weisel BA. Maternal mortality in the epidemic of Asian influenza New York City 1957. *Am J Obstet Gynecol* 1958;**76**:897–902.
15. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. *Clin Chest Med* 1992;**13**:679–691.
16. Knuttgen HG, Emerson Jr K. Physiological response to pregnancy at rest and during exercise. *J Appl Physiol* 1974;**36**:549–553.
17. Lederman MM. Cell-mediated immunity and pregnancy. *Chest* 1984;**86**(Suppl 3):6S–9S.
18. Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. *Br J Obstet Gynaecol* 1978;**85**:518–524.
19. Center of Disease Control and Prevention. Frequently asked question: is the use of ribavirin (or other antiviral drugs) effective in the treatment of patients with SARS? Available: <http://www.cdc.gov/ncidod/sars/faq.htm>.
20. Kochhar DM, Penner JD, Knudsen TB. Embryotoxic, teratogenic, and metabolic effects of ribavirin in mice. *Toxicol Appl Pharmacol* 1980;**52**:99–112.
21. Ferm VH, Willhite C, Kilham L. Teratogenic effects of ribavirin on hamster and rat embryos. *Teratology* 1978;**17**:93–101.
22. Chang CH, Chen KY, Lai MY, Chan KA. Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2002;**16**:1623–1632.
23. Wong RS, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ* 2003;**326**:1358–1362.
24. Choi KW, Chau TN, Tsang O, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med* 2003;**139**:715–723.
25. Tsui PT, Kwok ML, Yuen H, Lai ST. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. *Emerg Infect Dis* 2003;**9**:1064–1069.
26. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA. Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto Area. *JAMA* 2003;**289**:2801–2809.
27. Chan JW, Ng CK, Chan YH, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). *Thorax* 2003;**58**:686–689.

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