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ANATOMICAL PATHOLOGY

The placentas of patients with severe acute respiratory syndrome: a pathophysiological evaluation

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Summary

Aims: The pathology of the placentas delivered from pregnant women who had severe acute respiratory syndrome (SARS) in Hong Kong was studied.

Methods: The pathology of the placentas was retrospectively studied in detail and compared with control sets. The clinical data of the women and neonates were also reviewed.

Results: A total of seven placentas were studied. The placentas from two women convalescent from SARS in the first trimester were normal. In three placentas delivered in the acute stage of SARS, there were increases in intervillous or subchorionic fibrin which might be related to disturbances in maternal placental blood flow due to the hypoxic respiratory disease. Extensive fetal thrombotic vasculopathy (FTV) with sharply demarcated zones of avascular fibrotic villi was noted in the placentas of two patients convalescent from SARS in the third trimester. Both pregnancies had intrauterine growth retardation, oligohydramnios and newborns small for gestation. The aetiology of the FTV might be related to thrombotic tendency due to SARS or placental hypoxia.

Conclusions: This report highlights placental pathology that was probably the result of pathophysiological alteration of the maternal fetal unit during SARS. Further studies are required to delineate the relationship between severe maternal respiratory disease, placental pathology and pregnancy outcome.

Key words: Severe acute respiratory syndrome, SARS, placenta, pregnancy, pathology, fetal thrombotic vasculopathy.

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INTRODUCTION

An epidemic of severe acute respiratory syndrome (SARS) occurred in Hong Kong from March to June 2003. In total, 1755 individuals were infected and 300 died, giving a mortality of 17%.[1] SARS is a new form of atypical pneumonia caused by a coronavirus (SARS-CoV) and is spread mainly by respiratory droplets and through exposure to fomites. The disease was retrospectively recognised to occur first in the southern province Guangdong of China in November 2002.[2] Spread by travellers, major outbreaks occurred in China, Hong Kong, Vietnam, Singapore and Canada. Worldwide, more than 8000 individuals were infected, with an overall mortality of 9.6%.[3] SARS was most likely a zoonotic disease as a number of wildlife species, including the masked palm civet, have shown laboratory evidence of infection by a related coronavirus.[2] Based on the age and sex distribution of SARS, Anker has estimated that there were 100 pregnant women among the more than 8000 SARS cases reported worldwide.[4] The first reported cohort of five infants born to mothers with SARS showed no evidence of vertical or perinatal transmission of SARS-CoV. [5] The outcome of twelve pregnant women with SARS was reported by Wong *et al.*[6] and Lam *et al.*[7] The mortality rate of 25% was higher than that of the general population. Wong also showed that pregnant SARS patients had a higher rate of respiratory failure and drew an analogy with the more severe clinical course of epidemic influenza in pregnant women. This study was undertaken to examine the pathology of the placentas delivered from women who contracted SARS during pregnancy and to correlate the findings with the clinical and obstetric course and the neonatal outcome. This study can provide information about the pregnancy outcome and placental pathophysiology when pregnant mothers are affected by severe respiratory failure. The findings may provide clues to the optimal management of these patients, especially in view of an imminent epidemic of avian influenza.

METHODS

Princess Margaret Hospital is a tertiary care hospital with 1200 beds. It is the designated hospital for infectious diseases in Hong Kong. It was one of the designated hospitals for SARS during the epidemic and managed more than 700 SARS patients. It was also the only designated centre for the management of pregnant women with confirmed or suspected SARS. The Obstetric Department normally handles about 4000 deliveries per year. A few clinical series on SARS have been reported from this hospital including the five infants born to mothers with SARS and the twelve pregnant women with SARS mentioned in the introduction.[5–7] The outcomes and prognostic factors in 267 patients with SARS were also reported from this hospital.[8] The present study was a retrospective review of all the placentas delivered from women with confirmed SARS during pregnancy. In the clinical paper covering these patients, the pathology of these placentas has been briefly mentioned.[6] A confirmed diagnosis of SARS was based on the combination of clinical features, contact history and laboratory findings. The clinical features included body temperature of 38°C or higher and radiographic evidence of lung infiltrate with or without respiratory symptoms. The history required that there was contact with a patient with SARS or travel history to an endemic area within 10 days of symptom

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onset. The laboratory findings required a positive result on reverse transcriptase polymerase chain reaction (RT-PCR) or serological testing for SARS-CoV. The study period extended from March 2003 to March 2004. This covered the period when SARS was epidemic in Hong Kong (March to June 2003) and the subsequent nine months (July 2003 to March 2004), so that affected mothers could complete their deliveries. All placentas of SARS patients were notified and sent to the pathology department for pathological examination. Placentas from both mid-trimester abortion and delivery were included but uterine evacuation specimens from first trimester abortion were excluded. The fresh placentas were delivered to the pathology department with standard precautions after microbiological sampling in the delivery room. The specimens were fixed in 10% formalin for at least 48 h before examination. The placentas were examined by a standard protocol. The first author (WFN) was responsible for the initial or subsequent detailed pathological examination of all the case and control placentas. The placental weight was taken after trimming of the free membrane and cord. Serial sections of the placental disk $\leqslant 1$ cm thick were made. Blocks were taken from the membrane, cord, normal and abnormal area of the placental disk. At least two full-thickness blocks were sampled from the normal-appearing central area of the disk. Additional blocks were taken subsequently because of the unexpected findings of fetal thrombotic vasculopathy in two cases. Ten blocks of placental disk were examined for each case placenta (except for the last case, P7, in which four blocks were examined). The H&E sections were examined in detail. Comparisons with a reference set of placentas with known gestation and another control set of placentas were made to assess the morphological maturity of the villi and other microscopic features. Villous maturity that differed by at least 3 weeks from the gestational age was considered significant. The assessment of villous maturity was based on the proportion, size and capillarisation of mature intermediate villi and terminal villi. Because of the lack of a normal reference of placental weight with gestational age for the local Chinese population, the reference graph from Hall[9] was evaluated for the present study. A control set of placentas from non-SARS patients over the study period was collected. This set was chosen from the placentas routinely sent for pathological examination by the obstetrician, based on clinical indications. For each case placenta, two control placentas that matched exactly or within two weeks of the gestational age were chosen. The weights of the case and control placentas were plotted on the reference graph. When significant villous destruction was found, the functional or corrected placental weight was calculated. The percentage of placental destruction (infarct or avascular fibrotic villi) was estimated by combined gross and microscopic assessment of the placental slices. The functional or corrected placental weight was calculated by multiplying the placental weight with the factor of one minus proportion of placenta destroyed. The fetal to placental weight ratio was calculated and compared with the known reference published by Molteni.[10] Hospital records of the mothers and infants were reviewed by the first author (WFN). Correlation of the clinical information with the placental findings was made.

RESULTS

Over the study period, a total of 624 placentas from deliveries were examined. Another 58 placentas accompanied by the fetuses were examined from spontaneous or elective mid-trimester abortions. Seven placentas satisfied the study criteria. They were denoted as P1 to P7 in the chronological order that the placentas were received. This designation is used to refer to either the patients or the placentas in the subsequent text. The first placenta (P1) was received in early April 2003 and the last placenta (P7) was received in November 2003. The uterine curettage specimen from a 9-week pregnant SARS patient was excluded from the study. Table 1 summarises the clinical and pathological findings of these cases and details of the control placentas.

Clinical features of SARS

The age of the patients varied from 25 to 34 years with a mean of 29.7 years. The past health of all of these patients was unremarkable. All patients had fever, constitutional upset and radiological features of pneumonia. P1 to P6 had positive RT-PCR for SARS-CoV on respiratory or other specimens. These six patients received antibiotics, ribavirin and corticosteroid for treatment. Intravenous pulse methyl-prednisolone was given to patients P1, P2, P3 and P5. For P7, RT-PCR for SARS-CoV was negative but subsequent serology showed sero-conversion. The first three patients (P1 to P3) progressed to acute hypoxic respiratory failure in the first 2 weeks of admission. They required intensive care, intubation and mechanical ventilation with 100% oxygen. These three patients had emergency Caesarean delivery after stabilisation with mechanical ventilation. The remaining patients had delivery at the convalescent stage. P4 had mild shortness of breath requiring oxygen therapy (up to 4 L/min) for 9 days. Her oxygen saturation was intermittently down to 93% for 4 days with the lowest documented value at 91%. P5 had a more protracted clinical course requiring intensive care for 4 weeks and oxygen therapy (up to 10 L/min) for 21 days. Her oxygen saturation was down to 92–93% for 9 days with the lowest documented value at 89%. P6 and P7 had a stable clinical course and did not require oxygen. Other complications included hypotension (P1), acute renal failure (P3), raised activated partial thromboplastin time (APTT) and steroid psychosis (P4), disseminated intravascular coagulation (DIC) and SARS-CoV-associated hepatitis (P5). The diagnosis of DIC in P5 was based on raised prothrombin time (24.2 s, reference 10.0–13.0 s) and APTT ($>$120 s, reference 24–35 s). The platelet count was normal. Fibrinogen level, D-dimer or fibrin degeneration product were not checked. No clinical thromboembolism or bleeding was noted. The coagulation abnormality reverted to normal after four days. All patients went on to convalescence except for P1 and P2. Both died in the acute stage due to respiratory failure (P1) or superimposed methicillin resistant *Staphlococcus aureus* pneumonia (P2).

Obstetrical and neonatal courses

All of the patients were at the third trimester at the time of diagnosis of SARS except P6 and P7, who were in the first trimester, and all patients were of second gravidity except for P3 (gravidity 3) and P5 (gravidity 1). Their pregnancies were managed in different public hospitals or by private obstetricians before contracting SARS. Details of the previous antenatal records were not available. However, their previous and present obstetric histories were unremarkable, with uterine sizes corresponding to gestation on presentation. Daily cardiotocography (CTG) was performed for pregnancies after 28 weeks of gestation. Three patients (P1, P4, and P5) showed decreased variability of the baseline CTG tracing at the acute phase of SARS. Occasional variable deceleration was also noted in P5. When the first three patients deteriorated to acute hypoxic respiratory failure requiring ventilation, the risk of intrauterine death became imminent. Furthermore, the compromise of maternal respiratory function by the enlarged uterus was considered undesirable. Therefore, these three patients underwent emergency Caesarean

TABLE 1 Summary of clinical and pathological findings

Case	Stage of SARS at delivery Maternal complication	Gestation at SARS diagnosis (weeks)	Gestation at delivery (weeks)	Pregnancy complications	Apgar score Neonatal outcome	Fetal growth Fetal : placental weight ratio (95%CI)	Placental weight (corrected weight), g	Placental pathology	Control placentas: week/diagnosis/ placental weight
P1	• Acute • Respiratory failure requiring ventilation • Hypotension	27	28	• C/S on day 2 of ventilation • ↓ variability on CTG	5, 9 Prematurity	AGA 5.4 (4.3–6.0)	190	• Prominent intervillous fibrin	C1: 29/PP/270 C2: 28/IUGR/180
P2	• Acute • Respiratory failure requiring ventilation	32	32	• C/S on day 1 of ventilation	5, 9 Prematurity	AGA 6.6 (4.8–6.2)	250	• Prominent intervillous fibrin • Increased calcification	C3: 32/preterm/250 C4: 31/preterm/320
P3	• Acute • Respiratory failure requiring ventilation • Acute renal failure	26	26	• C/S on day 2 of ventilation	5, 7 Prematurity	AGA 5.1 (4.2–4.7)	190	• Focally prominent subchorionic fibrin	C5: 26/preterm/198 C6: 26/uterine rupture/220
P4	• Convalescent • Oxygen therapy for 9 days • Raised APTT • Steroid psychosis	28	33	• ↓ variability on CTG • IUGR • Oligohydramnios • Preterm labour	9, 10 Prematurity	SGA 8.2 (5.7–6.7)	170 (138)	• Accelerated villous maturation • Extensive avascular villi (19%)	C7: 33/PET/350 C8: 33/PROM/320
P5	• Convalescent • Oxygen therapy for 21 days • DIC • Hepatitis	30	37	• ↓ variability on CTG • IUGR • Oligohydramnios • C/S	9, 10 Uneventful	SGA 8.3 (6.5–7.5)	240 (199)	• Extensive avascular villi (8%) • Infarcts (9%) • Increased calcification	C9: 37/polyhydramnios/440 C10: 37/PROM/490
P6	• Convalescent • No oxygen required	12	15 (abortion)	• None • Elective termination	N/A	Normal abortus 1.3	75	• Increased calcification	C11: 17/Noonan syndrome/95 C12: 17/abortion/110
P7	• Convalescent • No oxygen required	3	38	• None	8, 10 Uneventful	AGA 7.4 (7.0–7.5)	410	Normal	C13: 38/PROM/450 C14: 38/fetal heart disease/460

AGA, appropriate for gestational age; APTT, activated partial thromboplastin time; CI, confidence interval for gestation; C/S, Caesarean section; CTG, cardiotocography; DIC, disseminated intravascular coagulation; IUGR, intrauterine growth retardation; PET, pre-eclamptic toxaemia; PP, placental previa; PROM, premature rupture of membrane; SARS, severe acute respiratory syndrome; SGA, small for gestational age.

section on the first or second day of mechanical ventilation. For the other patients, the pregnancy was not interrupted. At the convalescent stage, intrauterine growth retardation (IUGR) and oligohydramnios were noted in P4 and P5. For P4, the estimated fetal weight by ultrasound on presentation at 28 weeks was at the 25th percentile (about 1000 g). It dropped to below the 10th percentile at 33 weeks (about 1600 g), corresponding to about 31 weeks parameters only. Doppler study of the blood flow of the umbilical cord showed normal flow velocity. P4 had spontaneous preterm labor at 33 weeks and her intrapartum CTG was reactive. She had uncomplicated vaginal delivery. For P5, the estimated fetal weight on presentation at 30 weeks was at the 50th percentile (about 1400 g). It dropped to below the 10th percentile at 34 weeks (about 1500 g). Some catch-up growth was noted from 34 to 36 weeks (about 2000 g). At 36 weeks, the fetal parameters corresponded to that of about 32–33 weeks only. Doppler study of the arterial blood flow of the umbilical cord showed normal flow velocity with systolic to diastolic ratio of 2.6. She had spontaneous onset of labor at 37 weeks. Because of non-reassuring CTG, Caesarean section was performed. P6 elected to have termination of pregnancy at 15 week gestation. P7 had uncomplicated pregnancy, induction of labor at term and normal vaginal delivery. Because of the placental findings, P4 underwent thrombophilia screening about 17 months after delivery. There was no evidence of protein C, protein S or antithrombin III deficiency and lupus anticoagulant was not detected. P5 was not available for thrombophilia screening. Of the six deliveries, four were premature. The infants had birth weight appropriate for gestation except for P4 and P5 which had birth weights less than the fifth percentile. No infants had SARS on close monitoring and investigation. These infants were followed up in the high risk surveillance program. In particular, the babies of P4 and P5 showed normal development with no neurological deficit when last assessed at the age of 1 and 2 years, respectively.

Pathological findings of placentas

Figure 1 shows the weight of the case and control placentas plotted on the reference graph. From the distribution of the

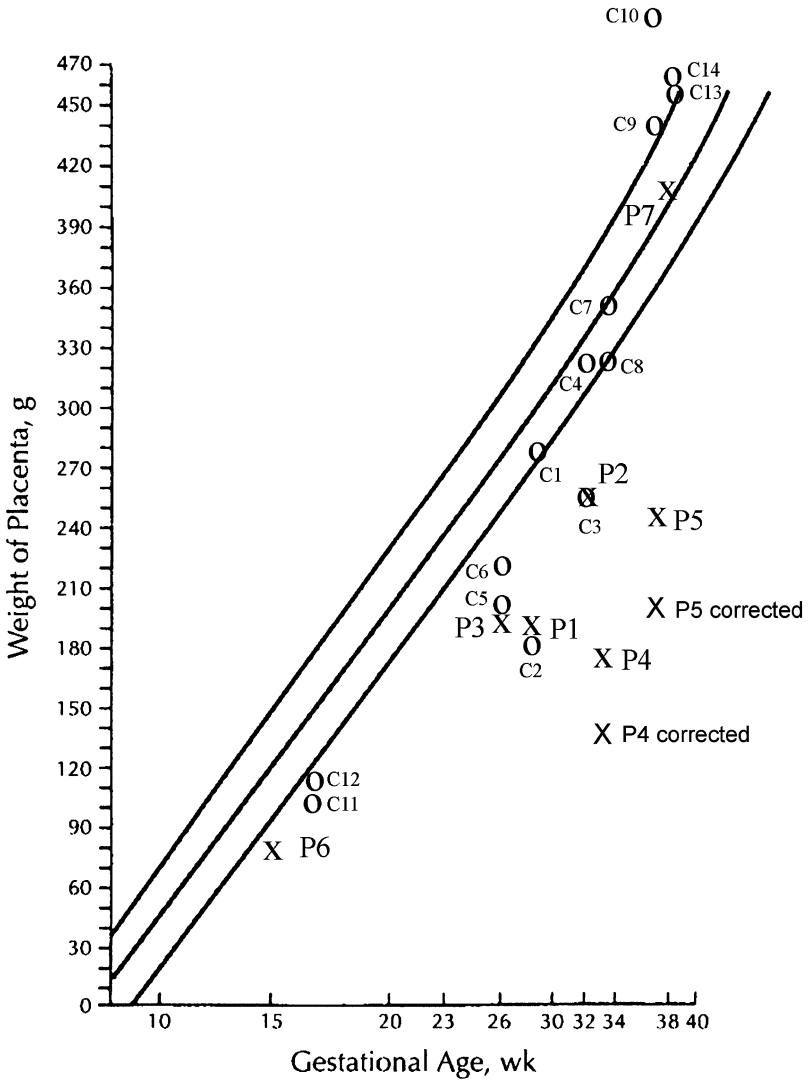

Fig. 1 95th–50th–5th percentile graph of placental weight (g) against gestational age (weeks). The case placentas (P1 to P7) are marked as X. The control placentas (C1 to C14) are marked as O. From the distribution of the plots, the graph appears applicable for the controls from about 30 week gestation. (Adapted version of figure 16.2 *Handbook of Normal Physical Measurements*[9] with permission from Oxford University Press, Oxford, UK.)

plots, the graph appears applicable for the controls from about 30 weeks onwards for the local Chinese population. The most abnormal placental weights were that of P4 and P5. Their corresponding fetal to placental weight ratios were also raised (Table 1). Figure 2 shows the gross morphology of the placental disks for P4 and P5. The microscopy of the placental disks is shown in Fig. 3 (P4) and Fig. 4 (P5). All the placental disks appeared grossly normal except for the presence of multiple old infarcts in P5, with the largest about 2 cm across (Fig. 2B). The total infarcted volume was estimated to be 9%. All the cords contained three vessels with no knots or other gross lesion. The cords showed either central or eccentric insertion.

Prominent intervillous or subchorionic fibrin was noted on microscopy in the three placentas delivered in the acute stage of SARS (P1 to P3). However, the gross appearance of these placentas was normal. In P1, small areas of perivillous fibrin were noted diffusely in the placenta with accentuation in the subchorionic and subdecidual zone. In P2 and P3, there were prominent subchorionic fibrin deposits. When compared with preterm placentas of similar gestation, the extent of the intervillous or subchorionic fibrin appeared increased. The most striking and unexpected histological abnormality was the occurrence of extensive avascular fibrotic villi in P4 and P5. Review of the placental disks showed only some subtle paler areas (Fig. 2). No thrombotic lesions were noted in the vessels of the chorionic plates. Because of this unexpected finding, all the case placentas were re-examined and re-sampled extensively. However, no additional cases with avascular fibrotic villi were noted. Ten blocks of placental disk were examined for each case except for P7 (four blocks examined only). The area of avascular fibrotic villi was carefully delineated on the slides and the percentage area of avascular villi was estimated (Fig. 2 insets). The percentage of avascular villi was estimated to be 19 and 8%, respectively, for P4 and P5. For P4, eight of the ten blocks of placental disk showed the presence of avascular villi. These foci were wedge-shaped, away from the peripheral margin of the disc, and always involved the decidual side of the placenta. Some were nearly full thickness and extended close to the chorionic plate. The area involved varied from 0.1 to 0.8 cm^2 (Fig. 2A inset). Both the artery and the vein in the stem villi at the apex of these foci appeared constricted and obliterated (Fig. 3A, right side of field). In the affected area, all the villi including stem villi, intermediate and terminal villi were avascular. Obliterated or collapsed vessels could still be identified in the stem villi and larger intermediate villi, but the smaller intermediate and terminal villi showed uniformly hyalinised stroma with no identifiable vessels (Figure 3C). There were increased syncytial knots. Scattered villi showed stromal and basement membrane calcification. There were also increased hemosiderin granules in the constricted vessels of the stem villi and the hyalinised stroma of the terminal villi, with accentuation in the trophoblastic basement membrane. When comparing the villous morphology of the avascular area with the vascular villi in the background, the former appeared to show a more immature appearance with more and larger intermediate villi and fewer and more plump terminal villi. The avascular villi did not show any abnormal shape or branching. The normal vascularised villi showed accelerated villous maturity with increased syncytial knots and increased capillarisation (Fig. 3B) when compared with a reference placenta of the corresponding gestation (Fig. 3D). Despite a gestation of 33 weeks, the villous maturity corresponded to that of 36–37 weeks (Fig. 3E, 4D). No organised thrombosis or other lesions were noted in the chorionic or umbilical vessels. In P5, the infarct and avascular villi occurred as separate non-contiguous lesions. Of the seven slides from non-infarcted areas, four showed the presence of avascular villi. This varied from 0.1 to 0.5 cm^2 (Fig. 2B inset). Thrombotic stem vessels were noted at the apex of these lesions (Fig. 4A, right side of field, and 4C). The morphology of the avascular hyalinised villi was similar to that of P4 (Fig. 4E). When P4 and P5 were adjusted for the avascular and infarcted villi, the functional placental weight dropped to 138 and 199 g, respectively, about 50% of the expected weight (Fig. 1; functional weight of P4, 138 g = placental weight 170 g × [100% − 19% avascular villi]; functional weight of P5, 199 g = placental weight 240 g × [100% − 8% avascular villi − 9% infarcted villi]). Increased villous calcification was noted in P2, P5 and P6. In P2 and P6, the calcification occurred in the perivillous fibrin in the subchorionic and subdecidual zone. In P5, besides increased calcification in the area of infarction and avascular villi, a more diffuse perivillous calcification was noted in the vascularised villi. As the case placentas were all beyond the first trimester (earliest P6 at 15 weeks), significant erythroblasts in the placenta were not expected. Erythroblasts in the range of 1–2 per high power field

Fig. 2 Gross morphology of representative slices of the placental disks of (A) P4 and (B) P5. P4 was grossly normal except for scattered subtle paler area (near centre of slice). P5 showed multiple infarcts (arrow head) and scattered subtle paler area. Both insets show H&E stained sections of the placental disks. The upper black lines represent the side of the chorionic plate. The area delineated by the closed black lines represents foci of avascular fibrotic villi. (The background grid unit is 1 cm. For the insets, the background grid unit is 2.5 mm.)

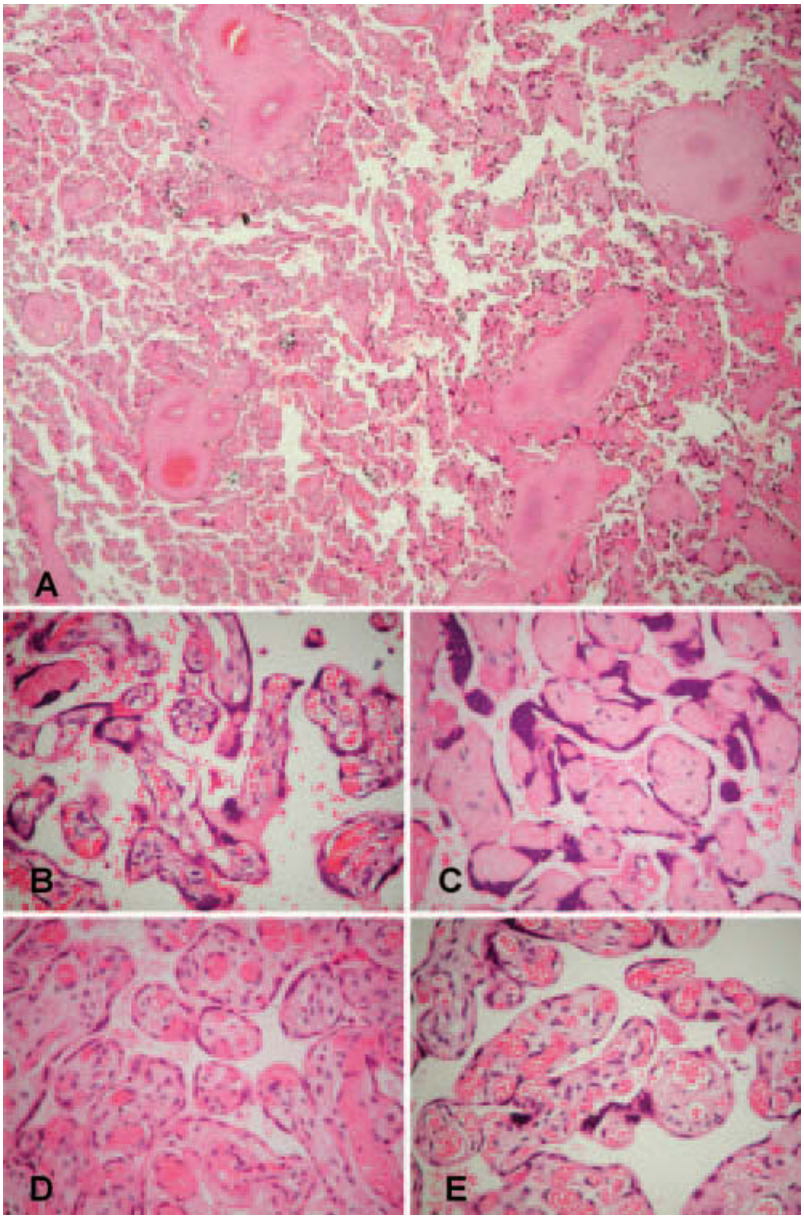

Fig. 3 Microscopy of the placental disk of P4 (33 week gestation). (A) Low power view with the chorionic plate on the upper side. Normal vessels of stem villi and terminal villi on the left compared with obliterated vessels of stem villi and avascular fibrotic terminal villi on the right. The demarcation between the two areas was sharp and in the middle of the field (H&E, ×20). (B–E) Morphology of terminal villi at the same magnification (H&E, ×100). (B) Background terminal villi of P4 showing increased capillarisation and increased syncytial knots compared with a reference 33 week placenta in Fig. 3D. The villous maturity was accelerated and comparable with that of a 36 week reference placenta in Fig. 3E and that of 4D (P5 placenta at 37 weeks). (C) Avascular fibrotic terminal villi of P4.

(HPF) in the large stem vessels were noted in P1 and P5. Erythroblasts of 3–4 per HPF were noted in P6. The other placentas showed no erythroblasts. No other pathology was noted in the case placentas. In particular, no villitis, chorioamnionitis, decidual vasculopathy or chorangiosis were noted. All of the cord vessels were unremarkable on sections. In the control placentas, infarct was noted in a 33 week placenta affected by pre-eclamptic toxaemia (C7). Accelerated villus maturity was noted in two placentas affected by pre-eclamptic toxaemia (C7) and premature rupture of membrane (C8, 33 weeks). Prominent inter-villous fibrin was noted in a 29 week placenta with placenta previa (C1). No control placentas showed fetal thrombotic vasculopathy or avascular fibrotic villi.

DISCUSSION

The pathology of the placentas of SARS patients has not been specifically addressed previously. Although there was an estimate of about 100 pregnant women with SARS,[4] there were only a few reports, 19 cases in total.[6,7,11–13] The cases reported, including the present series, are summarised in Table 2. The case fatality rate was three of 19 (16%). Six had spontaneous or elective abortion. Like many systemic diseases, SARS probably had an all-or-none effect on first trimester pregnancy. Of the remaining thirteen patients, six had deliveries in the acute stage and seven had delivery in the convalescent stage. There was intrauterine death of one twin in a convalescent patient (Case 3, Table 2), and this was likely to be related to the *in vitro* fertilisation rather

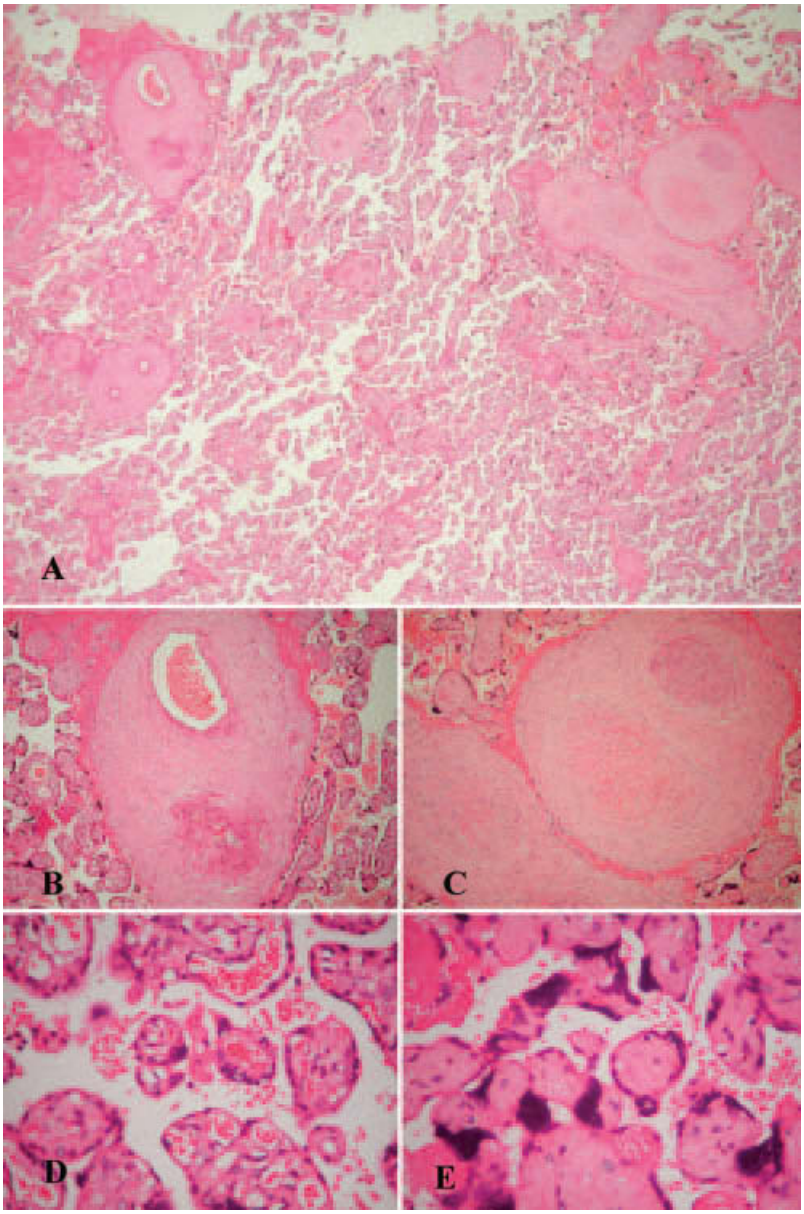

Fig. 4 Microscopy of the placental disk of P5 (37 weeks gestation). (A) Low power view with the chorionic plate on the upper side. Normal vessels in the stem villi and terminal villi on the left compared with thrombosed vessels on the stem villi and avascular fibrotic villi on the right (H&E, ×20). (B) Close up view of normal artery and vein of a stem villus (H&E, ×50). (C) Close up view of thrombosed vessels in a stem villus (H&E, ×50). (D) Background vascular terminal villi with term maturity (H&E, ×100). (E) Avascular fibrotic villi (H&E, ×100).

than SARS. IUGR and small-for-date newborns were noted in the present series only. Placental findings were reported only in the present series and from Case 6 of Table 2 which was normal. This current small study highlights placental pathology which may correlate with the clinical courses of the mother and fetus. As expected, the two patients convalescent from SARS in the first trimester (P6 and P7) had uneventful pregnancy outcome and normal placentas. The three patients (P1, P2 and P3) who had emergency delivery at the acute stage of SARS had placentas showing more prominent intervillous or subchorionic fibrin when compared with reference placentas. This was probably due to increased eddies or underperfusion of the maternal placental circulation as a result of the hypoxia and shock. The most unusual pathological change was the observation of extensive avascular villi and thrombotic fetal vessels in P4 and P5, which were placentas delivered in the convalescent stage following significant maternal disease. This pathology of fetal thrombotic vasculopathy (FTV) should be distinguished from other causes of avascular villi such as villitis. FTV has been associated with maternal diabetes,[14] coagulation disorders[15] and pre-eclampsia.[16] Diabetes and pre-eclampsia were absent in these two patients. Although P4 had isolated elevation of APTT for 2 days, there was insufficient evidence for DIC. The finding of isolated raised APTT with normal PT was actually noted in 63% of SARS patients in the first two weeks of illness.[17] Thrombophilia screening of P4 was normal. The cause for the extensive FTV was uncertain. In P5, the presence of DIC might explain the occurrence of both the placental infarct and FTV. The diagnosis of DIC in P5 was a clinical and

TABLE 2 Summary of reported cases of pregnancy complicated by SARS

Case no.	Stage of SARS at delivery/ abortion	Gestation at SARS diagnosis (trimester or week)	Gestation at delivery/ abortion (week)	Method of delivery	Fetal growth	Maternal outcome	Placental pathology	Reference (case number in original reference)
1	A	III	31	C/S for fetal distress	Twin, AGA	Alive	NR	11 (A)
2	C	III	38	C/S on request of relatives	AGA	Alive	NR	11 (B)
3	C	II	NA	Not available at the time of report	IUD of one twin at 23 wks	Alive	NR	11 (C)
4	A	III	38	Forceps for poor uterine contraction and fetal distress	AGA	Alive	NR	11 (D)
5	A	40	40	C/S for fetal distress	AGA	Alive	NR	11 (E)
6	C	20	38	C/S for placenta previa	AGA	Alive	Normal	12
7	C	31	39	Vaginal	AGA	Alive	NR	13
8–11	A or C	3–5	2–5 weeks later	(Spontaneous abortion)	–	One death	–	6 (1–4)
12	C	6	10	(Elective abortion)	–	Alive	–	6 (5)
13	A	27	28	C/S for maternal respiratory failure	AGA	Death	↑ Fibrin	*P1/6 (12)
14	A	32	32	C/S for maternal respiratory failure	AGA	Death	↑ Fibrin	P2/6 (11)
15	A	26	26	C/S for maternal respiratory failure	AGA	Alive	↑ Fibrin	P3/6 (10)
16	C	28	33	Vaginal	SGA	Alive	FTV	P4/6 (8)
17	C	30	37	C/S for non-assuring CTG	SGA	Alive	FTV	P5/6 (9)
18	C	12	15	(Elective abortion)	–	Alive	↑ Calcification	P6/6 (6)
19	C	3	38	Vaginal	AGA	Alive	Normal	P7/6 (7)

*Present series (P1 to P7).
A, acute; AGA, appropriate for gestational age; C, convalescent; C/S, Caesarean section; CTG, cardiotocography; FTV, fetal thrombotic vasculopathy; IUD, intrauterine death; NR, not reported; SARS, severe acute respiratory syndrome; SGA, small for gestational age; II, III (trimester 2, 3).

tentative one, as more definitive tests of DIC were not performed. The placental findings might be taken as evidence in support of the presence of DIC. In comparison, Cases 2, 6 and 7 in Table 2 had a similar gestational stage at the onset of SARS as P4 and P5; however, the obstetrical courses were normal and the fetuses showed normal growth. Case 6 showed respiratory failure and was ventilated for 1 week. Cases 2 and 7 had mild transient hypoxia (oxygen saturation of Case 7 down to 92% for a short time) and oxygen therapy but did not require intensive care. The more protracted clinical course with more persistent hypoxia in P4 and P5 might explain the unfavourable obstetric outcome.

To explain the FTV in the placentas of the two SARS patients, coagulation disorders need to be considered. Although in animal studies coronavirus could induce phlebitis and thrombosis,[18] clinical thromboembolism or DIC were not prominent features of SARS.[8] In one series of 157 SARS patients, DIC occurred in only four patients in association with severe respiratory failure, multiorgan failure and superimposed bacterial infections.[17] In post-mortem series, minor thromboembolism was found in some patients.[8,19] Avascular necrosis of bone was reported in convalescent SARS patients. Magnetic resonance screening of 1117 SARS patients from Hong Kong after 6 months convalescence showed the presence of subchondral avascular necrosis in 12.1% and intramedullary infarcts in 3.2%.[20] The patient's co-morbidity, respiratory status during the SARS infection and the dose of corticosteroid received were noted to correlate with the incidence of avascular necrosis. The association of thromboembolism with SARS might require further study.

Redline has suggested that transient decrease in flow or hypoxia during gestation might prematurely trigger the reflex of constriction of the specialised spiral folds in the fetal arteries in the placenta (folds of Hoboken) and lead to fetal thrombosis.[21] The uterine blood flow might decrease with systemic vasodilatation due to shock. The lowering of the oxygen saturation to about 90% in SARS patients would significantly decrease the oxygen partial pressure from the normal 100 mmHg to about 75 mmHg. Coupled with the simultaneous drop in maternal placental blood flow, these changes might cause significant placental hypoxia. While the overall fetal oxygen supply might be maintained by increased oxygen uptake by the fetal circulation, selective shunting due to hypoperfusion could result in regional placental hypoxia. This hypoxic-induced vasoconstriction if persistent for a few hours might lead to thrombosis or permanent collapse and might be the underlying cause of the FTV in P4 and P5. As the vasoconstriction would occur in both the maternal and fetal circulation, the lack of maternal placental infarct in P4 might implicate that the fetal circulation was more vulnerable to thrombosis. If this hypothesis is true, any severe respiratory or systemic diseases that result in significant and persistent maternal hypoxia in the third trimester might induce FTV in the placenta. However, such association has not been reported in the literature. Further study is needed to substantiate this hypothesis.

For the placentas P4 and P5, the functional weights were only about 50% of the expected. The placenta P4 (33 week gestation) showed more advanced villous maturity by increased capillarisation to that of term placentas. This reflected the physiological adaptation of the preterm placenta to increased functional demand. This adaptation appeared effective to withstand the stress of labour and vaginal delivery. On the other hand, P5 at a gestation of 37 weeks with only about 50% functional placental mass and maximum villous capillarisation of term placenta was unable to withstand the stress of labour and required Caesarean delivery. These two cases support the estimation that the placenta has about a 50% reserve over a slowly

developing insufficiency and also illustrate that labour and delivery draw on the placental reserve.

The placenta as the 'blackbox' of pregnancy may provide useful information to guide the management of severely ill pregnant women with hypoxia. This is of particular relevance in view of the persistent threat of further outbreak of SARS and the emerging new infection of avian influenza. Additional studies will be needed to further delineate the relationship between severe maternal respiratory disease such as SARS and avian influenza, placental pathology and pregnancy outcome.

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