INTRODUCTION

Severe Acute Respiratory Syndrome (SARS) is a highly infectious disease with significant morbidity and mortality. The first reported index case in Hong Kong was admitted to hospital on 22nd February 2003. As of May 4, a total of 1629 cases in Hong Kong have been diagnosed with SARS, including 184 deaths. It is too early to calculate a mortality rate because a significant number of patients remain in critical condition. SARS has also affected 5 pregnant women beyond 24 weeks of gestation, with two deaths reported to date. It has also affected at least 5 cases in the first trimester in Hong Kong. Obstetricians and gynaecologists may encounter pregnant women with SARS in their practice. The following are guidelines issued by the Hong Kong College of Obstetricians and Gynaecologists based on the current understanding of the disease. Readers are also encouraged to access relevant websites for updated information about the disease (Appendix I).

DIAGNOSIS

The World Health Organization (WHO) and the Centers for Disease Control and Prevention, United States of America (CDC) both have published case definitions of SARS. The recommendation is for all patients and there is no reason that pregnant subjects should be different.

The case definitions by the WHO are developed to describe the epidemiology of SARS and the terms ‘suspect’ and ‘probable’ cases are used. As of May 1, 2003, they are defined as follows:

A ‘suspect’ case is a person presenting after November 1, 2002 with history of high fever >38°C and cough or breathing difficulty. In addition, the person should have one or more of the following exposures during the 10 days prior to onset of symptoms: 1. close contact with a person who is a suspect or probable case of SARS; 2. history of travel to an area with recent local transmission of SARS; 3. residing in an area with recent local transmission of SARS.

A person is also considered a ‘suspect’ case of SARS if he or she has an unexplained acute respiratory illness resulting in death but on whom no autopsy has been performed and had one or more of the following exposures during the 10 days prior to onset of symptoms: 1. close contact with a person who is a suspect or probably case of SARS; 2. history of travel to an area with recent local transmission of SARS; 3. residing in an area with recent local transmission of SARS.

A ‘probable’ case is defined as a suspect case with one or more of the followings: 1. radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome on chest X-ray; 2. positive result(s) for SARS coronavirus by one or more assays, 3. autopsy finding consistent with the pathology of respiratory distress syndrome without an identifiable cause.
A person should be excluded as a suspect or probable case of SARS if an alternative diagnosis can fully explain their illness.

The case definition by CDC[^1] is similar to that of the WHO and was last updated on April 30, 2003. The main difference between CDC’s definition and that of WHO is the starting date of the illness. CDC counts cases presenting after February 1, 2003 instead of November 1, 2002. Both the WHO and CDC defined ‘close contact’ as having cared for, lived with, or direct contact with respiratory secretions and/or body fluids of a patient known to be a suspect SARS case. Affected areas are defined by national health authorities of respective countries.

To date, the case definitions by both the WHO and CDC are on clinical and epidemiological basis. The identification of coronavirus on laboratory assays help in the diagnosis but is not yet an essential criteria. The reason is that a reliable and widely available diagnostic test for infection with the SARS coronavirus has yet to be found[^2]. However, with increasing knowledge of this disease and the development of reliable laboratory assays for the causative agent, the definitions may need to be updated accordingly.

3 MANAGEMENT

3.1 General comments

Many aspects about the illness, such as the pathophysiology, possible modes of transmission and the appropriate medical treatment, remain unclear. According to the current knowledge, SARS can be considered as a contagious infection caused by a novel coronavirus and transmitted through droplets and close contact. It primarily affects the respiratory system causing atypical pneumonia, with some rapidly progressing to acute respiratory distress syndrome. The clinical spectrum of the disease is also unclear.

In a cohort of asymptomatic inhabitants of Amoy Garden in Hong Kong, positive PCR for coronavirus has been identified in nasopharyngeal swabs. The significance of asymptomatic carriers is unknown.

3.1.1 Effect of pregnancy on SARS infection

Whether pregnancy itself carries any adverse effect on the course of SARS is unknown. Theoretically, the physiological changes in pregnancy, in particular, increased oxygen consumption, cardiac workload and metabolism[^4], would put additional stress on SARS patients. There is also reduced cellular immunity in the second half of pregnancy[^5]. Based on the experience with adult respiratory distress syndrome complicating pregnancy, the maternal mortality is as high as 24.4%[^6]. Of the 5 pregnant SARS patients presenting at 26-32 weeks of gestation in Hong Kong, 4 required admission to intensive care unit and 2 have already died because of septic shock and respiratory failure respectively.

3.1.2 Effect of SARS on fetus and pregnancy

Transplacental passage of the virus and perinatal infection may be an issue. Congenital infection has not yet been confirmed in the 3 babies delivered from SARS pregnant women in Hong Kong. However, the diagnosis of congenital infection could be difficult. The diagnostic test currently available is not sensitive enough to detect the virus until the late stage of infection and it is clinically difficult to differentiate between respiratory distress syndrome due to prematurity and that due to SARS infection. Other risks include prematurity (if the infection occurs in preterm gestation) and cerebral palsy. Based on the experience of acute respiratory distress syndrome unrelated to coronavirus infection in pregnancy, maternal deterioration leading to respiratory failure is a risk factor for preterm labour and perinatal asphyxia[^7]. The side effects of medical treatment also present some concern to the fetus.
3.2 Admission and issue of infection control

One of the central issues in the care for SARS patients is infection control. Health workers are at high risk of infection and of cross infection of each other, especially in a hospital setting. A designated team consisting of obstetricians, midwives, anaesthesiologists, neonatologists and supporting staff has to be set up in each obstetric unit that looks after pregnant SARS patients. The team members must be thoroughly familiar with the infection control protocols, which should be regularly reviewed and amended for improvement.

There should be designated ward area and delivery suite, where all pregnant women with SARS are admitted. Infected subjects must not be referred to ordinary antenatal clinic, antenatal ward or labour suite. The designated team should be contacted before transfer of such patients.

Strict infection control must be practiced and policed at all times in these designated wards. Personal protective equipment including surgical mask or N95 mask, googles or visors, cap, protective gown and gloves must always be worn prior to entry into these wards. A detailed description of infection control measures can be found in Appendix II.

3.3 Current medical management and its safety

Currently, all modalities of medical treatment are empirical. The most commonly used first-line medications in Hong Kong are ribavirin and corticosteroids. However, the value of these 2 drugs especially ribavirin has been questioned. It is therefore very important to form a liaison team with the physicians who are most updated with the effective treatment of this condition. As ribavirin and corticosteroids are the two most commonly used medications, safety of their use in pregnancy is discussed below:

3.3.1 Ribavirin

Ribavirin is a nucleoside analogue of guanosine and acts as an anti-viral agent by inhibiting replication of RNA and DNA viruses. It is categorized as a class ‘X’ drug based on the US FDA categorization of risk of drug use in pregnancy (Category X: Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant). Significant embryocidal and teratogenic side-effects of ribavirin have been reported in animal studies, including limb abnormalities in hamsters, craniofacial defects in rats, neurological and ocular abnormalities in mice and embryocidal effect in rabbits. However, when exposed to high doses of ribavirin, no adverse fetal outcomes were seen in baboons, which is the only primate model studied thus far.

Data on the exposure of ribavirin in human pregnancy is scanty and no adverse neonatal effects have been attributed to the drug to date. In one case report, ribavirin inhalation therapy was given to a woman at 33 weeks of gestation as a form of treatment for her severe influenza. Caesarean section was performed after 4 hours’ treatment because of maternal deterioration. The child had normal physical examination at one year of age. In another case series, nine pregnant patients suffering measles were treated with ribavirin between 20-38 weeks of gestation. One of these 9 patients had a termination of pregnancy because of deteriorating maternal condition. No adverse neonatal outcome was noted in the remaining 8 patients. Of these 8, ribavirin was given at 23-24 weeks of gestation in 2 pregnancies and at between 32-38 weeks of gestation in the other 6.
3.3.2 Corticosteroids

High dose corticosteroids either in the form of intravenous hydrocortisone at a dose of 4 mg per kg body weight every eight hours \(^8\) or oral prednisolone at a dose of 1 mg per kg \(^9\) have been used. In patients with persistent fever or worsening lung condition, pulsed methylprednisolone at a dose of 500 mg daily may also be given \(^9\). All corticosteroids cross the placenta to a varying degree. The maternal-fetal concentration of prednisolone is 10:1 \(^18\), compared with 6:1 in hydrocortisone and 3:1 in betamethasone \(^19\). With such a high dose of prednisolone, a significant level of glucocorticoid activity would be produced in the fetal compartment. This has generated concern on the potential harmful effects of prolonged high dose of steroids on the growing fetus, in particular restriction of intrauterine growth, altered brain development and adverse programming of the fetal hypothalamic-pituitary-adrenal axis \(^20,21\). Despite this concern, experience from the use of prednisolone in pregnant patients with autoimmune diseases suggests that obvious adverse neonatal outcome is uncommon.

The high glucocorticoid activity in the fetal side has been thought to bring about surfactant production and hence beneficial effects on the fetal lung. However, previous studies on antenatal methylprednisolone using a dose of 125 mg daily has failed to demonstrate any reduction in the incidence of respiratory distress syndrome (RDS) in preterm infants \(^22,23\). It has been proposed that despite a very high peak level, there is rapid clearance and hence this regimen would not provide a sustained elevation of glucocorticoid activity necessary for induction of proteins responsible for maturation \(^24\).

3.4 Antenatal management

The management of pregnant women with SARS will depend on the maternal condition, the gestational age, the fetal well-being and the maternal wish. A multidisciplinary approach involving physicians, obstetricians, neonatologists, anaesthesiologists and midwives is very important. The primary concern should be the mother’s safety and hence, any treatment considered to be useful should not be withheld because of uncertain fetal risk unless an alternative is available. However, in any case, the patient and/or her husband should be counseled about the benefits and potential fetal risk of the medical treatment. Specific considerations at different gestations are listed below:

3.4.1 Before 24 weeks of gestation

If the use of ribavirin is considered necessary by the physician, the patient should be made aware of the potential teratogenic side-effects of the drug and the limited information on its use in human pregnancy. The option of termination of pregnancy (TOP) should be discussed. The concern of teratogenicity is higher in the first trimester when fetal organogenesis takes place. It has to be noted that ribavirin may still cause functional defects and minor malformations even after the first trimester.

In general, if TOP is decided, it is preferred to have it performed after the infection has been successfully treated. It is possible that some cases will have the TOP delayed from the first trimester to the second trimester but this should not be a major concern. However, as the course of the illness is very variable and it may take several weeks for some cases to recover, medical TOP performed at around the time of treatment of SARS can be considered if the gestational age is more advanced than 20 weeks. This will ensure a successful termination of pregnancy before 24 weeks of gestation. In any case, the life of the mother remains the first priority and the decision of the timing of TOP should be a conjoint decision with the physician. Termination of pregnancy should always be delayed if judged to be inappropriate by the physician in view of the critical maternal condition.
3.4.2 24-33 weeks of gestation

Fetal viability is reached after 24 weeks of gestation and hence delivery for fetal reason is an additional consideration although the maternal health takes precedence. The potential adverse effect of pregnancy on the natural course of SARS and the potential fetal risk related to the maternal clinical condition and the medical treatment have to be balanced against the morbidity and mortality related to preterm delivery. The decision of delivery has to be individualized. Given the high neonatal risks of preterm delivery and that many SARS patients respond to medical treatment, continuation of pregnancy is favoured provided the maternal condition allows, especially <32-34 weeks.

In view of high-risk for preterm delivery, one course of antenatal corticosteroids in terms of betamethasone or dexamethasone should be prescribed to hasten the fetal lung maturity as there is inadequate data to suggest that prednisolone is effective in reducing RDS. However, the safety and regime of corticosteroids should be discussed first with the physicians to ensure it is not contraindicated in the state of viraemia or too much steroids have been used.

Apart from the routine antenatal care, special attention should also been given to the followings:

(a) keep the oxygen saturation above 95% to maintain adequate oxygen supply to the fetus;

(b) maintain the maternal temperature below 38 degree Celcius, if possible, as the fetal temperature is 1-1.5 degree Celcius higher than the mother;

(c) regular fetal surveillance for fetal distress and intrauterine growth retardation.

3.4.3 After 34 weeks of gestation

The risk of neonatal complications is low if delivered after 34 weeks of gestation. The threshold for delivery should therefore be lower as the gestational age advances. However, it is contentious whether elective delivery should be offered once 34 weeks of gestation is reached, especially when the mother is stable. The advantages of elective delivery are: (1) the mechanical factor of a large gravid uterus can be removed; (2) the physiological stress related to pregnancy can be gradually alleviated; (3) delivery under control can be offered before maternal and fetal demise as deterioration can be very rapid. The arguments against an elective delivery include: (1) induction of labour or caesarean section and its associated anaesthesia carry significant risk to the mother in the presence of pneumonia; (2) delivery in the presence of maternal viraemia pose risk of perinatal infection as the newborn will invariably inhale or swallow some maternal body fluids at delivery; (3) some pregnant women would respond to the medical treatment without the need for early delivery, speaking from the limited experience of managing SARS pregnant women in Hong Kong.

Given the current knowledge on this disease is so limited, it is unknown whether elective delivery would offer benefit to the woman and the baby. Both decisions are acceptable. Joint discussion with the physicians, anaesthesiologists and the neonatologists are important for the decision in each individual case. It is also important to inform the patients of the pros and cons of the decision. In general, patients who show stable clinical condition without oxygen desaturation might be candidates for continuation of pregnancy. Those with poor response to medical treatment or with signs of deterioration should warrant consideration of early delivery.
3.5 Delivery

If termination of pregnancy is decided, surgical method should be offered for early gestation below 13 weeks and medical method with prostaglandins should be used for more advanced gestation.

If delivery is required because of deteriorating maternal condition, caesarean section is preferred. Induction of labour is not advisable because of the risk of failed induction, especially in the presence of unfavourable cervix in preterm gestation, and the inappropriateness of a long labour in the presence of critical maternal condition. Vaginal delivery can be considered if the patient is in labour and maternal condition permits.

Currently there is no clear evidence that any mode of anaesthesia is superior for pregnant SARS patients. All patients should be considered at risk for prolonged postoperative ventilatory support, depending on the degree of preoperative respiratory dysfunction, residual effects of general anaesthetic drugs and postoperative wound pain. General anaesthesia poses high risk of cross infection to staff during tracheal intubation. Regional anaesthesia carries the theoretical risk of spreading viral infection into the cerebrospinal fluid and the central nervous system, although the virus might have already been present in the central nervous system before the procedure. The final decision on the mode of anaesthesia should therefore be made by the anaesthesiologist after consideration of the clinical condition of each individual case. Epidural analgesia in labour may be considered but may be precluded by limitations of resources in isolation areas.

Termination of pregnancy and delivery (vaginal or caesarean) are also considered ultra-high risk of cross infection for healthcare workers. Precaution should be particularly made against transmission of infection by splash of body fluid or blood during delivery. All TOPs and deliveries should be performed in designated delivery suite or theatre for SARS patients, preferably with negative pressure ventilation. Special arrangement, for example, special passage, is needed to avoid spread the disease during transfer of patients to the operating theatre from the ward. All involved staff should have the similar level of protection as in the case of intubation of SARS patients. Disposable instruments are preferred.

To reduce perinatal infection, the baby should have early clamping of umbilical cord and early cleansing to facilitate removal of maternal blood and liquor.

Paediatrician and the neonatal nursery should be informed of the delivery once it is decided so that preparation can be made. All babies born to mothers with SARS or have had SARS infection should be regarded as potentially infectious until more data concerning perinatal infection is available. They should be admitted to isolation rooms at neonatal nursery until infection can be confidently excluded.

3.6 Postnatal management

The patient should be isolated from her baby until she has recovered and is no longer infectious.

It is not known if the virus is excreted from breast milk and breastfeeding should be avoided until further information is available.

Ribavirin has long plasma half-life and it may take a long time for the drug to be eliminated from the body after multiple dosage. There is a concern that ribavirin may persist in gonadal tissue. Therefore, after recovery, contraception is advised for 6 months if ribavirin has been used although there was one report of favorable neonatal outcome when a woman conceived 3.5 months after discontinuation of ribavirin.
4 REMARK

The guidelines are prepared with the current understanding of SARS infection and the limited experience of managing SARS pregnant women. With the growth of the knowledge concerning this condition, it is likely that the guidelines need to be regularly updated.

REFERENCE LIST


ACKNOWLEDGEMENT:

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Appendix I: Relevant web-sites about SARS
(The list covers most relevant web-sites but is not exhaustive)

Appendix II: Guidelines for infection control procedures - ULTRA HIGH RISK areas (ICU, & other SARS isolation areas)

1. **Handwashing** - wash hands promptly and thoroughly with hand antiseptic (e.g. Hibiscrub) after patient handlings, and especially after contact with blood, body fluids, secretion and excretions, and after removing gloves and gowns. Alcoholic hand-rub can be used where handwashing facilities are not readily available.

2. **Gloves** - put on disposable gloves (e.g. latex gloves) when entering isolation area, and wash hands upon removal of gloves.

3. **Masks** - staff should properly apply N95 respirator covering both nose and mouth. Patients should wear surgical masks.

4. **Gowns and protective apparel** - staff should wear gowns whilst in the isolation area. They must be removed upon leaving the isolation area.

5. **Goggles / visors / eye protection** – should be worn for direct patient contacts, particular care is needed for aerosol generating procedures (e.g. intubation, suction), and for procedures likely to generate splashes of blood, body fluids, secretions or excretions. They can be disinfected with hypochlorite solution diluted 1:50 (1,000 ppm) for 15 min. after use.

6. **Surgical Helmet shield** – Surgical Helmet shield (eg. 3M Air-mate System) can be considered for procedures such as caesarean section or delivery.

7. **Patient care equipment** - contaminated, reusable items should go through proper disinfection / sterilization procedures before recirculation for communal use.

8. **Disposal of potentially infected items:**
   
   A/ **Linen/Laundry** - treat all used linens as potentially infectious according to hospital guidelines.

   B/ **Urinal & bedpan** - urine and faeces should be carefully poured into sewage. Wash and disinfect containers using bedpan disinfecter (80 – 85°C) or disinfect by immersing in hypochlorite solution of (1000ppm) dilution for at least 15 mins.

9. **Waste handling** – In addition to the current hospital clinical waste management protocol, all wastes arising from patient diagnosis and treatment, dressing & swabs, items contaminated with patients’ secretions & excretions should be placed in red bags with white tag for special treatment.

10. **Specimen handling** - apply Universal Precautions, and follow existing practices. For microbiology specimens (e.g. Nasal Pharyngeal Aspirate), ensure that primary containers are securely sealed and place specimen upright in transport box or place specimen in sealed plastic bag in transport box.

11. **Environment** - routine thorough cleansing (once per duty shift), paying particular attention to surfaces around the patient, using hypochlorite solution 1000ppm.

12. **Visitors** – not permitted in SARS isolation areas. If a special arrangement is made for visitation on discretionary grounds, N95 masks, gloves, caps and gowns must be worn by visitors. Discourage close contact of visitors with patients.