Invited Review

Major Pulmonary Disorders Leading Intensive Care Unit Admission in Pregnancy

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Respiratory insufficiency is one of the most frequent causes of intensive care unit (ICU) admissions among obstetric patients. The challenges faced in the treatment of this patient population are even greater due to the fact that there are two young lives to be saved simultaneously: mother and fetus. Any treatment which may be the best choice for the mother may adversely affect the fetus. The aim of this review is to summarize the reasons and the management of the most common pulmonary disorders requiring ICU admissions in pregnancy for the obstetrician. In the spectrum of this review the most common reasons of respiratory failure such as bronchial asthma, pulmonary embolism, amnion fluid embolism and pneumonia will be discussed. Optimal management for all of the disorders requires early identification and treatment of the respiratory failure, stabilizing the hemodynamics, improve oxygenation and close fetal and maternal monitoring.

Key Words: Respiratory failure, Pregnancy

Gynecol Obstet Reprod Med;14:2 (139 - 143)

Respiratory insufficiency is one of the most frequent causes of intensive care unit (ICU) admissions among obstetric patients.[1,2] The incidence is reported between 25 to 45 %.[1,3] The aim of this review is to summarize the causes and the management of the most common pulmonary disorders requiring ICU admissions during the pregnancy for the obstetrician. In the spectrum of this review management of bronchial asthma, pulmonary embolism, amnion fluid embolism and pneumonia will be discussed.

Asthma

The most common pulmonary disease during the pregnancy is asthma because of the high prevalence in the general population. Poorly controlled asthma in pregnancy can lead to several adverse outcomes including increased prematurity, low birth weight and preeclampsia. It also may result in serious complications such as fetal hypoxemia and increased risk of perinatal mortality.[4]

Inadequate use of medication is an important reason of asthma exacerbation in pregnancy.[5,6] Studies performed in pregnant asthmatics indicated that fetal outcome is improved by appropriate use of medications and avoidance of acute exacerbations.[7]

As mentioned above, the therapy of asthma exacerbation should be initiated immediately in a pregnant patient. Although none of the antiasthma drugs belongs to Pregnancy Risk Category A, which is defined as the highest level of safety according to the Food and Drug Administration (FDA), asthma guidelines suggest the appropriately monitored use of theophylline, inhaled corticosteroids, beta 2 agonists and leucotriene receptor antagonists in pregnancy in order to prevent the proven risks of acute exacerbations.[8]

The principles of the management of asthma exacerbation in pregnant women are not different from the non pregnant patients but some important points should be emphasized:

1. The patient and the fetus should be monitored,

2. Patient should be examined in a sitting position in order to prevent supine hypotensive syndrome,

3. Oxygen supplementation should be given to maintain oxygen saturation at > 95 %,

4. The initial treatment should include the administration of inhaled albuterol every 20 minutes up to three doses,

5. Ipratropium bromide (500 µg) should also be administered in severe cases,

6. Systemic corticosteroids should be given to patients whose symptoms did not improve with the initial bronchodilator therapy and to those with moderate to severe exacerbation. Budesonide and beclametasone should be the preferred choices,

7. Intravenous aminophylline has not been shown to have additional bronchodilator effects,

8. If necessary, arterial blood gas analysis should be performed. The compensated respiratory alkalosis in pregnant pa-

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Submitted for Publication: *25. 06. 2008*
Accepted for Publication: *30. 06. 2008*

tients should be kept in mind. Worsening of alkalosis may lead to fetal hypoxia, conversely respiratory acidosis may also develop even a $PaCO_2$ level more than 28-32 mmHg in a pregnant patient. Therefore, any changes in pH should be corrected urgently,

9. If the patient is dehydrated, intravenous fluids should be administered.

10. Oral/ parenteral administration of beta 2 agonists is not advised because of the lack of safety during the first trimester, the potential inhibitory effect on the delivery and the frequently observed side effects such as tachycardia and tremor,

11. Systemic administration of epinephrine should be avoided because of its vasoconstrictor effect on the uteroplacental unit.[9-11]

Pulmonary Embolism

Venous thromboembolism (VTE) and pulmonary thromboembolism (PTE) are the leading causes of mortality and morbidity in pregnancy. It has been reported to occur in 1-2 of 1000 pregnancies but it is estimated that the true incidence is much more than this figure. Nonspecific symptoms and reluctance to use diagnostic tests because of the fear of radiation exposure are the main reasons of underestimation of the disease.[12] It can occur at any time during the pregnancy but it is more frequently seen during the antenatal period. Risk factors for VTE include prior history of VTE, presence of an inherited thrombophilia or family history of thrombophilia, obesity, recent trauma or surgery, immobilization, age older than 35 and multiple gestations.[13]

Clinical suspicion is critical for the diagnosis of PTE. Since many of the symptoms of embolic disease such as dyspnea, tachypnea and tachycardia may also be present during the normal pregnancy, the diagnosis should be confirmed with objective tests.[12] Routine laboratory tests including whole blood count, electrocardiogram and chest radiograph should always be performed for a patient with PTE suspicion to exclude other potential causes of the patient's symptoms. D-Dimer testing has a questionable role in the diagnosis of PTE in the pregnant because numerous clinical conditions including pregnancy itself may increase D-Dimer levels.[14] It is reasonable to perform primarily bilateral lower extremity Doppler ultrasound for a patient with suspected deep vein thrombosis.[15] If the result is positive treatment should be initiated. If the ultrasound is negative but clinical suspicion continue further testing is needed in order to evaluate suspected PTE. These tests are V/Q scan, helical CT, pulmonary angiogram and chest radiograph which can safely be used in pregnant.[15-17]

V/Q scanning is an appropriate first step in the diagnosis of PTE in pregnancy. If V/Q scanning is used during pregnancy, it is preferred to perform perfusion scanning alone first, since this procedure decreases the radiation exposure for the fetus and mother.[18] PTE can be safely ruled out for the patients with normal V/Q scan. Patients with high probability of V/Q scan should be treated for PTE. In the case of non diagnostic V/Q scan, PTE cannot be excluded.

Helical CT scan is an alternative diagnostic choice among patients with suspected PTE however the use in pregnancy has not been validated yet. Another advantage of CT scan is to visualize the other possible causes of the clinical symptoms when PTE is absent. Echocardiography may also be useful in supporting the diagnosis of PTE.

Pulmonary angiography, although an invasive procedure which requires expertise, it has been considered as the gold standard for the diagnosis of PTE in pregnant women. It should be reserved for only in suspicious cases.

Heparin is the mainstay of the therapy for PTE during pregnancy because it does not cross the placenta in contrast to warfarin, which can cause fetal hemorrhage and malformations. Either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) can be used[12,19] Although LMWH is advantageous in terms of fixed dosing and potentially lower incidence of heparin induced thrombocytopenia and osteoporosis, monitorization of anti Xa levels are required.[20-22]

Pregnant patients with acute PTE should receive intravenous heparin for 5 days followed by subcutaneous heparin treatment at the remainder of the pregnancy and 6 weeks postpartum. Pregnant patients may require higher doses of heparin to achieve therapeutic level. Increased heparin requirements may be due to increased levels of heparin binding proteins, heparin degradation of placenta, plasma volume and renal clearance due to elevated glomerular filtration.[23,24] Minimum starting therapeutic doses of LMWH in pregnancy should be enoxaparin 1 mg/kg or dalteparin 100 IU/kg sc BID. If the diagnosis is certain, a slightly higher dose is required. Dosing should not be less frequently than every 12 hours.[24] The therapeutic range of antifactor Xa for LMWH use is 0.5- 1.0 IU/ml (3-4 hours after injection). Target international normalized ratio (INR) is 2.0- 3.0 for the patients treated with UFH. UFH or LMWH should be discontinued 24 hours before the expected time of delivery.[19]

Anticoagulation may be insufficient for the therapy among patients with massive PTE. Therefore supportive care and intravenous anticoagulation should be initiated as soon as possible. If hypotension persists despite the patient is in left lateral decubitis position and adequate volume resuscitation, vasopressor therapy should be initiated with remembering the lower blood pressure levels due to pregnancy.[25] Dopamine is the first choice vasopressor agent in pregnancy.

Since pregnancy is considered as a relative contraindication, the experience with thrombolytic therapy is limited.

Although some case reports indicate the use of thrombolytics safely during pregnancy, there are no prospective randomized controlled trials yet.[26,27] Inferior vena cava (IVC) filters have been successfully used during pregnancy and the indications are the same as for the nonpregnant patients.[28] Embolectomy is the last choice treatment option for massive PTE when conservative therapy failed. Although data are lacking, it has been successfully used for the selected cases in which PTE is life-threating.[29,30]

Amnion Fluid Embolism

Amniotic fluid embolism (AFE) is a rare but catastrophic syndrome characterized by abrupt cardiorespiratory collapse and coagulopathy during labor and immediately postpartum. Risk factors of AFE are turbulent labor, trauma, multiparity, oxytocin use, increased maternal age, increased gestational age, male fetus, cesarean section and eclampsia .[31,32]

The pathogenesis of AFE is still unclear but it has been proposed that amniotic fluid enter the maternal venous circulation through the endocervical veins at a placental site or due to uterine trauma.[33]

The classic presentation of the disease is hypoxia, hypotension, altered mental status, disseminated intravascular coagulation (DIC) and shock. Other common symptoms include seizures, agitation, evidence of fetal distress and constitutional symptoms such as fever, chills, nausea, vomiting and headache.[34] Some of the case reports also noted anaphylaxis due to AFE.[35]

The diagnosis of AFE depends on the clinical findings and exclusion of the other diseases with similar signs and symptoms.[34] Although hypoxia, hypotension, pulmonary edema and DIC have been reported as common symptoms, fetal distress may also be the only initial symptom of AFE.[32]

There are no diagnostic laboratory tests for the diagnosis of AFE. The white blood cell count may be elevated as an acute phase reactant. Thrombocytopenia is a rare finding. Bilateral interstitial and alveolar infiltrates distributed bilaterally can be observed due to pulmonary edema. The ECG may show tachycardia, ST and T wave abnormalities or findings of right ventricular overload.[34]

Treatment of AFE is usually supportive. At first, the patient should be transferred to the ICU unit and monitorized including respiratory and cardiac monitoring. If the patient has not delivered yet, a continuous fetal monitoring should also be performed. The most important goal of the therapy is to prevent additional hypoxia and those related mortality and morbidity. Additionally treating hypotension with adequate fluid resuscitation and vasopressors in order to keep urine output > 0.5 ml/kg/h and mean arterial pressure >65 mmHg, treating left ventricular dysfunction with inotropic therapy, treating DIC and coagulopathy with fresh frozen plasma (FFP), cryoprecipitate, fibrinogen and factor replacements. Moreover treating hemorrhage with red blood cell (RBC) transfusions and thrombocytopenia with platelets are essential.[33,34,36] Immediate delivery may be taken into account for near term fetus in order to prevent further hypoxemic damage. Seizures should be treated with antiepileptic medications. There should be never a delay in the administration of advanced cardiac life support medications because of fear of fetal toxicity.

The prognosis of disease is poor according to both fetal and maternal outcome. The maternal mortality is reported between 29.5- 61 % but unfortunately the risk of sequelae is extremely high among survivors.[32,37]

Pneumonia

Pneumonia is the most frequent cause of mortality in pregnancy among non-obstetric infections.[38] The estimated prevalence ranges from 1.1 to 2.2 per 1000 deliveries and is not different from that in nonpregnant adults.[39,40] The onset of pneumonia is not gestational age dependent but maternal physiologic changes due to pregnancy make pneumonia less well tolerated.[41]

The microorganism causing pneumonia in pregnancy is not different from those nonpregnant populations. *Streptococcus pneumonia* is the most common identified pathogen followed by *Haemophilus Influenzae*.[39] Viral and fungal pathogens also must be kept in mind.

Clinical symptoms including fever, cough, pleuritic chest pain, dyspnea and tachypnea are not different from those nonpregnant patients. Inspiratory crackles may occasionally heard because of the compression atelectasis secondary to the the elevated diaphragm. Sputum gram staining and culture should be performed in order to identify the etiological agent. Blood culture should be taken in severe cases, although it is rarely reported positive. A chest radiograph is necessary for both the pneumonia and the differential diagnosis in pregnant patients.[42]

The management of pneumonia in pregnancy includes early diagnosis, initiation of the antimicrobial therapy, evaluation of the mother and fetus for oxygenation and maintenance of normal respiratory function.[43] Although none of the antimicrobial agents are licensed for use in pregnancy, macrolide and beta lactam antibiotics are recommended because of the favorable safety profile and coverage of the most common pathogens. Quinolones, tetracycline, chloramphenicol and sulpha compounds are contraindicated in pregnancy.[44] Infectious Disease Society of America and American Thoracic Society guidelines recommend treatment with macrolide antibiotics for mild illness with addition of beta lactam for severe disease. In patients at an increased risk of hospital acquired pneumonia or aspiration pneumonia, an additional aminoglycoside use for coverage of pseudomonas and enteric

gram negative organisms should be considered bearing in mind the risk of fetal toxicity to the auditory nerve.[42]

In addition to antimicrobial therapy, it is essential to maintain maternal PaO_2 of > 60-70 mmHg and oxygen saturation > 95 % with the lowest possible oxygen supply.[45] Indications of ICU admission and intubation include inadequate oxygenation (PaO_2 of < 60 mm Hg or oxygen saturation < 85 % on % 60 fraxionated inspired O_2), inadequate ventilation ($PaCO_2$ > 50 mmHg), inable to protect airway, sepsis requiring invasive hemodynamic monitoring or persistent metabolic acidosis.[45-47]

In conclusion, management of the pregnant patients requiring ICU admission due to respiratory failure is challenging and requires a multidisciplinary team approach. Optimal management requires early identification and treatment of the respiratory failure, stabilizing the hemodynamics, improve oxygenation and close fetal and maternal monitoring. If the patient is near term, ICU must be prepared for delivery. As difficult intubation is relatively common in obstetric patients, it is essential to be aware of the condition in order to decrease risk of preventable death. Unfortunately, little information is available about the reasons and treatment of respiratory failure in pregnancy.

Gebelikte Yoğun Bakım Tedavisi Gerektiren Solunum Sistemi Hastalıkları

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Gebelerde solunum yetmezliği yoğun bakım gereksinimlerinin en sık nedenlerini oluşturmaktadır. Gebe hastanın yoğun bakımda tedavisi diğer hastalardan çok daha zordur çünkü hem anne hem de bebeğin hayatı genellikle tehlike altındadır. Anne için en iyi olabilecek bir tedavi seçeneği bebeği olumsuz yönde etkileyebilir. Bu derlemenin amacı, gebelerde yoğun bakım tedavisi gerektiren solunum yetmezliği nedenlerinin ve bu nedenlere yaklaşımın özetlenmesidir. En sık görülmesi nedeniyle bronşial astım, pulmoner emboli, amniyon sıvı embolisi ve pnömoni bu derlemede irdelenen başlıklardır. Tüm bu hastalıklarda en uygun genel yaklaşım solunum yetmezliğinin erken tanısı ve tedavisi, hemodinamik bulguların stabilizasyonu, oksijenizasyonun düzeltilmesi ve hem anne hem de bebeğin yakın monitorizasyonudur.

Anahtar Kelimeler: Solunum yetmezliği, Gebelik

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