Acute respiratory diseases in pregnancy

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Abstract

Pregnant women are known to have an increased morbidity and mortality for certain illnesses due to physiological and immunological changes in pregnancy. However, careful attention should be paid to the fetoplacental unit, with delivery generally indicated for obstetric purposes only. Acute respiratory distress syndrome is an uncommon condition in pregnant patients. An essential component in the management of this condition is a perfect coordination between the obstetrician, the pneumologist and critical care specialists. Pregnancy-associated venous thromboembolism consists of deep vein thrombosis and pulmonary embolism occurring during pregnancy or in the postpartum period. This condition is common and is a major source of morbidity in a population which is young and otherwise relatively healthy. Amniotic fluid embolism remains one of the most devastating conditions in obstetrics practice, with reported mortality of 20% to 60%. The treatment is mainly supportive and involves the delivery of the fetus when indicated, respiratory support and hemodynamic support, with the judicious use of fluids, vasopressors, inotropes and, in some cases, pulmonary vasodilators. Respiratory failure complicates a relatively small number of pregnancies, but carries significant potential risks for both mother and fetus. The causes of respiratory failure may be related to pregnancy-specific conditions or other respiratory diseases, and the management requires a multidisciplinary team approach, involving obstetrics, maternal-fetal medicine, neonatology, obstetric medicine, pulmonology and critical care.

Keywords: *pregnancy-associated venous disorders, respiratory failure, pneumonia, amniotic embolism, ARDS*

Rezumat

Este cunoscut faptul că femeile gravide sunt expuse unei morbidităţi şi mortalităţi crescute din cauza unor modificări respiratorii şi imunologice asociate sarcinii. De aceea, această categorie de paciente trebuie să beneficieze de o atenţie sporită în ceea ce priveşte mama, cât şi fătul. Afecţiunile acute respiratorii se întâlnesc relativ rar în sarcină. O componentă esenţială a managementului acestora o reprezintă perfecta coordonare dintre obstetrician, pneumolog şi medicul specialist în terapie intensivă. În cadrul afecţiunilor tromboembolice în sarcină sunt incluse tromboza venoasă profundă şi embolismul pulmonar, care pot apărea atât pe parcursul sarcinii, cât şi în lăuzie. Această afecţiune este relativ frecventă, fiind o sursă majoră de morbiditate la o populaţie tânără şi altfel sănătoasă. Embolia cu lichid amniotic rămâne una dintre cele mai devastatoare condiţii patologice la pacientele gravide, având o mortalitate raportată de 20-30%. Tratamentul este în principal suportiv şi implică naşterea imediată a fătului, suport respirator şi hemodinamic, cu utilizarea judicioasă a fluidelor, substanţelor vasopresoare, inotrope şi în unele situaţii a vasodilatatoarelor. Insuficienţa respiratorie complică un număr relativ mic de sarcini, dar comportă riscuri importante atât pentru mamă, cât şi pentru făt. Cauzele de insuficienţă respiratorie pot fi reprezentate de afecţiuni respiratorii specifice sarcinii sau afecţiuni nespecifice sarcinii apărute pe perioada acesteia, managementul lor necesitând o echipă pluridisciplinară în care să fie implicaţi obstetricieni, specialişti în medicină materno-fetală, neonatologi, pneumologi şi medici specialişti în terapie intensivă.

Cuvinte-cheie: *afecţiuni tromboembolice venoase asociate sarcinii, insuficienţă respiratorie, pneumonie, embolie amniotică, ARDS*

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Introduction

Pregnancy significantly modifies the physiology of maternal respiratory system. Elevated progesterone levels stimulate the respiratory center, creating a functional state of hyperventilation. In the meanwhile, the gravid uterus alters lung volumes, determining the maternal perception of dyspnea[(1)]. Moreover, during pregnancy, a decreased cytotoxic lymphocytic activity has been noticed[(1)]. All of the aforementioned modifications aim to realize a successful adaption of the maternal organism for the maintenance of pregnancy, but they can be detrimental to the maternal well-being.

Pneumonia

Pneumonia is an ongoing and prevalent problem among elderly and immunosuppressed people; in pregnant women it represents the third leading cause of death, and also the most common non-obstetric infectious cause of death in women[(1)]. A correlation between pneumonia in the third trimester of pregnancy and preterm labor has been proved, that may lead to hypoxia and acidosis, poorly tolerated by the fetus. Therefore, pneumonia exposes the pregnant woman and her unborn child to a significant risk[(1)].

Community-acquired pneumonia (CAP) is recognized as a common condition that carries a substantial

morbidity and even mortality. The extreme ages are usually affected, while its occurrence in non-pregnant young women is rare. Nevertheless, pneumonia in young adults can be severe and fatal[2]. By contrast, in the pregnant women, pneumonia is the most frequent cause of fatal non-obstetric infection[3].

CAP increased frequency during pregnancy can be explained by the complex alterations of the cellular immunity that allows fetal allograft. These changes include decreased lymphocyte proliferative response, especially in the second and third trimesters, decreased natural killer cell activity, changes in T cell populations, with a decrease in the numbers of circulating T helper cells, reduced lymphocyte cytotoxic activity, and production by the trophoblast of substances that can block the maternal recognition of fetal major histocompatibility antigens[4,5]. In addition, the hormones prevalent during pregnancy – including progesterone, human chorionic gonadotropin, alpha-fetoprotein and cortisol – may inhibit cell mediated immune function[6]. These changes could theoretically increase the risk for infections, particularly with viral and fungal pathogens.

CAP in pregnancy may be difficult to diagnose by clinicians, its symptoms being mistaken with those of pregnancy-related physiological respiratory changes, but also due to the discrete clinical appearance of the symptoms. Moreover, patients themselves may attribute symptoms of pneumonia exclusively to pregnancy, therefore delaying the medical diagnosis. For example, dyspnea is a symptom extremely common during pregnancy, being experienced by 50% of women at 19 gestational weeks (GW) and up to 76% at 31 GW[7].

Bacterial pneumonia is an unusual cause of serious illness in pregnant women. In the past, the prognosis of a woman with pneumococcal pneumonia was significantly worse than for a non-pregnant person. However, with the wide availability of antibiotics, this difference in prognosis no longer exists.

Streptococcus pneumoniae is the most common organism identified, followed by *Haemophilus influenzae*. Because the likelihood of pneumococcal infection is so high in patients with community-acquired pneumonia, penicilins are the first line of treatment. Penicilins are considered to be safe for administration in pregnant women; all of them pass through the placenta, but none are harmful either to the fetus, or to the newborn[10,12]. An alternative therapy must be administered to the penicillin-allergic patient. If the patient's penicillin hypersensitivity is of the immediate type (anaphylaxis or urticaria), erythromycin is a safe substitute, both for the mother and the fetus. As a rule, cephalosporins are not usually administered in patients with known immediate reactions to penicillins; however, if the penicillin allergy has been manifested as a late reaction, such as skin rash, cephalosporins may be given[11,12].

The infection with *Legionella* spp. has also been documented, but it is rare[8]. Based on the few cases reported, it is generally felt that there is no increase in the risk of infection during pregnancy, and possibly no difference in the severity of the disease. The treatment with erythromycin has proved successful[8,9].

Among viral pneumonias, those determined by influenza are the most frequently encountered. Pregnant women are considered to be at risk for developing the severe form of the disease during pandemic or epidemic influenza infections, beside children, old patients, patients with underlying chronic respiratory and cardiovascular conditions[13]. Three antigenically distinct types of myxoviruses known to determine the human disease – types A, B and C – have been described; type A is usually associated with epidemic disease and, historically, it has been implicated in causing severe disease in pregnant patients. The mortality was the highest in women in the third trimester[9].

Two classes of influenza antivirals are available: the adamantane M2 ion channel inhibitors (amantadine and rimantadine), and the neuraminidase inhibitors (oseltamivir and zanamivir)[15].

During the 2009 pandemic, the Centers for Disease Control and Prevention (CDC) recommended for the first time the use of antiviral drugs for all pregnant women with influenza and prophylactically to those with significant influenza exposures[16]; the recommendation was based on previous studies which proved that the maximal efficacy in non-pregnant women was achieved when the antiviral medication was given prior or in the early phase of a viral infection[17]. The exact efficacity of the aforementioned drugs in the severe forms of the disease in pregnant women is not known. Despite incomplete data, recommendations for post-exposure prophylaxis and early initiation of treatment for pregnant women suspected of influenza infection are important components of strategies to reduce morbidity and mortality[18].

Both natural infections and vaccination with inactivated influenza vaccine (TIV) can generate robust maternal antibody responses that can be transfered transplacentally (IGG antibodies)[19]. Interestingly, TIV determines equivalent antibody titers in pregnant and non-pregnant women, the influenza-specific maternal transplacental antibody transfer occurring in up to 99% of pregnant women after the TIV administration[19]. TIS is licensed for use during pregnancy in the United States of America.

The prevention of influenza infections in pregnant women and their newborns begins with efforts to limit exposures, including hand washing, respiratory hygiene, cough etiquette, and the implementation of infection control precautions and environmental procedures in the healthcare settings which these individuals frequent. Pregnant women with suspected influenza should not be left in waiting rooms with uninfected pregnant women and should be triaged quickly for rapid examination, diagnosis and treatment. If hospitalized, droplet precautions should be instituted, and all persons coming within three feet of the woman should wear a surgical mask. The education of family members, as well as of pregnant women is a very important component of

prevention. This becomes even more important once the baby is born, as proper hand hygiene prior to handling the baby is an essential component of preventing the transmission to the newborn[21].

Pneumonia with varicella virus (VZV) was also associated with an adverse outcome in pregnant women. Up to 40% of pregnant women with varicella virus pneumonia require mechanical ventilation, the mortality in these patients ranging from 3% to 14% with antiviral therapy. Varicella can have a severe evolution in adults and probably even worse in pregnant women[22]. The exposure of the baby to the virus just before or during delivery poses a serious threat to the neonate, which may develop a fulminant neonatal infection (neonatal varicella). Rarely, these neonates can develop disseminated visceral and central nervous system disease, which is commonly fatal. The neonatal infection occurs primarily when the symptoms of maternal infection occur less than five days before delivery to two days after. Varicella virus related pneumonia is usually treated with acyclovir, a synthetic nucleoside analogue that inhibits the replication of human herpes viruses, including VZV.

Acyclovir crosses the placenta readily and can be found in fetal tissues, cord blood, as well as in the amniotic fluid. Acyclovir can potentially limit the transplacental passage of the virus by inhibiting viral replication during maternal viremia[23].

Although **fungal pneumonias** are uncommon, it seems that coccidioidomycosis is more likely to disseminate in pregnancy, particularly during the third trimester. This condition may be caused by the impaired cell-mediated immunity, as well as by a stimulatory effect of progesterone and 17-beta-estradiols on the fungal proliferation. Amphotericin is the accepted therapy for disseminated coccidioidomycosis, a drug that is considered to be safe in pregnancy. The data for prolonged use of triazoles or for echinocandins in pregnancy are either insufficient, or suggest harm to the fetus[24,25].

Acute respiratory distress syndrome in pregnancy

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight and a loss of aerated tissue. The clinical hallmarks of ARDS are hypoxemia and bilateral opacities on chest radiography, while the pathological hallmark is diffuse alveolar damage (i.e., alveolar edema with or without focal hemorrhage, acute inflammation of the alveolar walls, and hyaline membranes)[26].

The frequency of ARDS in the general population is estimated to be 1.5 per 100,000 per year, with a fatality rate of 35-50%. Although no studies clearly elucidate the frequency of ARDS in the obstetric population, the incidence is believed to be similar to the general population. The prevalence of obstetric patients requiring intensive care in the UK and USA is 0.9%[27].

Despite advances in medical technology, ARDS is extremely lethal. In ARDS patients, certain clinical conditions are frequently predisposing factors for developing the syndrome[28].

Two types of potential injuries can determine direct or indirect injury lung. Direct lung injury includes pneumonia, aspiration pneumonitis, inhalation injury, pulmonary contusion, fat emboli and reperfusion injury, whereas indirect injury includes sepsis, trauma, acute pancreatitis, disseminated intravascular coagulation, burns, head injury, and blood transfusion related[29].

During pregnancy, non-obstetric causes for ARDS include sepsis due to pyelonephritis, pneumonia, intracerebral hemorrhage, blood transfusion and trauma. Pregnant patients are vulnerable to develop aspiration pneumonitis during labor, termed Mendelson syndrome[30]. The particular digestive physiological modifications, such as decreased lower esophageal sphincter tone, delay in gastric emptying and increased intraabdominal pressure, have a facilitating effect for aspiration of stomach contents during labor and delivery. Although the incidence of this complication has declined due to the improvements in anesthesia and increased use of regional anesthesia with caesarean section, aspiration pneumonitis is still an important cause of maternal morbidity[29].

An ARDS patient has clinical signs of acute hypoxemic respiratory failure: dyspnea, orthopnea, tachypnea and tachycardia[26]. Arterial hypoxemia refractory to the oxygen supplementation is a characteristic feature of ARDS. Chest auscultation reveals diffuse crackles and/or wheezing. Arterial blood gases typically show an initial decrease in both partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$). As the condition worsens, PaO_2 will decrease further, but $PaCO_2$ may increase if the patient is no longer able to maintain adequate ventilation. The chest radiograph is usually significant for bilateral diffuse alveolar and interstitial infiltrates.

The first and immediate goal is to maintain adequate maternal oxygenation (PaO_2>70 mmHg or 9.3 kPa; equivalent to an oxygen saturation of 95%) using oxygen supplementation to avoid the fetal effects of maternal hypoxia. Noninvasive positive pressure ventilation (NIPPV) can improve oxygenation when supplemental oxygen has failed, and in severe cases mechanical ventilation may be necessary[26].

The mechanical ventilatory support for the treatment of ARDS is essential, the goal being to rest the fatigued respiratory muscles while providing suitable gas exchange. Respiratory muscle rest involves invasive or noninvasive mechanical support; the ventilator must overcome pressures related to airway resistance and elastic properties of the lung to allow adequate ventilation and gas exchange.

In the management of ARDS, a variety of pharmacological therapies have been investigated. Corticosteroid use has been controversial, particularly with respect to the dose and timing of administration. The improvements in oxygenation have been reported

with the use of low to moderate dosing of methylprednisolone (<2.5 mg/kg/day)[31,32].

Uteroplacental perfusion is usually compromised in such situations, which may be catastrophic, depending on the amount of fetal oxygen reserve. ARDS is often preceded by sepsis and often terminates in maternal death, despite aggressive intervention. Inflammatory responses, complement activation and prostaglandins have been implicated as probable mediators for both sepsis and ARDS. Invasive hemodynamic monitoring and mechanical ventilation are usually warranted to provide a detailed assessment and support[33].

Pulmonary embolism in pregnancy

Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality during pregnancy and postpartum, remaining a diagnostic and therapeutic challenge[34]. Pregnancy determines a hypercoagulable state, pregnant patients being at risk for venous thromboembolism, a condition that includes pulmonary embolism (PE) and deep vein thrombosis (DVT). In the general population, acute PE has an estimated mortality of approximately 15% at three months[35], but is higher in patients hospitalized with massive PE (50%).

The key elements of Virchow's triad – including venous stasis, hypercoagulability and vascular damage – are all present during pregnancy and 6-week postpartum. Venous stasis typically begins in the first trimester and reaches its peak around 36 WG. It is manifested through dilation of capacitance vessels and diminished venous return due to pressure of the gravid uterus on the iliac veins[35]. Additionally, both vaginal and caesarean deliveries lead to tissue damage around the pelvic vessels and subsequent alteration of the vascular endothelium[36].

Few data are available on the use of thrombolytic therapy in pregnancy, pregnant women being usually excluded from clinical trials[35]. Moreover, no controlled studies have been performed[35]. While pregnancy is listed as a relative contraindication to systemic thrombolytic therapy, the high mortality rates associated with PE may urge for immediate intervention. Current guidelines on the thrombolytic use in PE stipulates that systemic thrombolytics are indicated when hypotension, defined as a systolic blood pressure <90 mmHg, is present in the absence of a high bleeding risk[37]. Systemic thrombolytic therapy can also be considered in patients with a low bleeding risk whose clinical status deteriorate after the initiation of anticoagulant therapy, prior to the development of hypotension.

Thrombolytics can be classified into three groups based on similar characteristics. First generation agents, including urokinase and streptokinase, are not fibrin-specific and function by converting plasminogen to plasmin. These agents also have shorter half-lives compared to later agents, requiring longer infusion times of 12-24 hours for the treatment of PE. Alteplase, a second-generation agent, is fibrin specific, meaning it works in the presence of fibrin. Its longer half-life allows for the administration over two hours. The third generation agents, including reteplase and tenecteplase, are fibrin-specific, as well[38].

Overall, available case reports documenting thrombolytic use for the treatment of massive PE in pregnant women suggest that the use of these agents is associated with beneficial outcomes and a relatively low risk of complications. However, the quality of evidence remains low and there is a potential for publication bias. According to the current guidelines, hypotensive patients or those presenting a deterioration of the clinical status after the onset of anticoagulant therapy may benefit from thrombolytic therapy[39].

Amniotic fluid embolism

Amniotic fluid embolism (AFE) is an acute, severe and devastating complication in obstetrics. The clinical presentation is abrupt onset of hypoxia, hypotension, seizures, or disseminated intravascular coagulopathy (DIC), occurring during labor or delivery, caused by the inflow of amniotic components into the maternal circulation[40].

To date, one diagnosis of AFE is clinically consistent with acute hypotension or cardiac arrest, acute hypoxia, or coagulopathy in the absence of any other potential explanation for the signs and symptoms observed[41]. This clinical diagnosis is essentially exclusion based on the clinical presentations that resemble both embolism and anaphylaxis[42].

The pulmonary manifestations of hypoxia seem to result from an initial period of profound shunting often followed (in survivors) by lung injury patterns consistent with acute respiratory distress syndrome (ARDS). Coagulopathy is the third leg of the classic triad of signs and symptoms comprising the AFE syndrome[43].

A review of multiple registry series founds a wide range of conflicting conclusions regarding the presence of identifiable risk factors for AFE. In general, reported risk factors for AFE include conditions in which the exchange of fluids between the maternal and fetal compartments is more likely, such as caesarean delivery, instrumental delivery, cervical trauma, *placenta praevia* and placental abruption. The association of induction of labor and AFE is inconsistently reported. Abnormalities of uterine tone are described commonly in cases of AFE. However, based on the investigations of maternal-fetal exchange, the frequency of oxytocin or other uterine simulants use, and the rarity of AFE, most investigators struggle to find a causative link between induction medications and AFE[44]. AFE is considered by some authors as a non-specific maternal response to fetal antigen, an severe acute inflammatory response determined by the activation of proinflammatory mediators[45].

To conclude, the diagnosis of AFE is primarily based on the clinical observations. The classic triad of sudden onset of hypoxia, hypotension and coagulopathy, with onset during labor and delivery within 30 minutes postpartum forms the hallmark of AFE diagnosis[44,46].

Acute respiratory failure in pregnancy

Respiratory failure affects up to 0.2% of pregnancies, more commonly in the postpartum period. Altered maternal respiratory physiology affects the assessment and management of these patients.

Acute respiratory failure with need of ventilator support is rare in pregnant patients. Less than 2% of women in the peripartum period need treatment in the intensive care unit (ICU). The main diseases that lead to ICU admission in non-developing countries are hypertensive diseases, hemorrhage and sepsis. Respiratory failure is a common complication of these and other diseases in the obstetric or postpartum patient, therefore respiratory failure is one of the main indications for ICU admission[47].

Hormonal changes in pregnancy affect the upper respiratory tract and cause airway hyperemia and edema[48]. The diaphragms are displaced upwards by up to 4 cm, but the potential loss of lung volume is offset by widening of the antero-posterior and transverse thoracic diameters. Functional residual capacity (FRC) decreases by 10% to 25% by term[48]. The vital capacity remains unchanged, and total lung capacity decreases only minimally. The measurements of airflow (forced expiratory volume – FEV1) and lung compliance are not altered during pregnancy, but chest wall and total respiratory compliance are reduced in the third trimester[50].

Respiratory failure may result from pregnancy-specific conditions, such as preeclampsia, amniotic fluid embolism or peripartum cardiomyopathy[51]. Pregnancy may increase the risk or severity of other conditions, including thromboembolism, asthma, viral pneumonitis and gastric acid aspiration[51].

The endotracheal intubation in the pregnant patient carries considerable risk. Failed intubation is eight times more common in the obstetric population than another anesthetic intubation[52]. The reduced FRC and increased oxygen consumption in pregnancy cause rapid oxygen desaturation during apnea or hypoventilation. Upper airway mucosal edema and friability can adversely affect visualization and increase the risk of bleeding. Nasal intubation should be avoided, and a smaller size endotracheal tube may be required[53]. Preoxygenation is important, but overventilation and respiratory alkalosis must be avoided. The risk of aspiration should always be considered[53].

Noninvasive ventilation is well suited to short-term ventilatory support and avoids the potential complications of endotracheal intubation and the associated sedation. This modality plays a role in obstetric respiratory complications which reverse rapidly[54].

Prolonged mechanical ventilation of pregnant patients in the ICU is relatively uncommon, and few data are available to guide management. Hyperventilation and alkalosis should be avoided in order to prevent uterine vasoconstriction. Blood gas abnormalities may adversely affect the fetus. Maternal oxygen saturation is only one factor contributing to fetal oxygenation, placental perfusion usually playing a more significant role[55]. While excessive hypocapnia may cause fetal harm by reducing placental perfusion, the effects of hypercapnia on the fetus are less clear. Maternal CO_2 levels are normally reduced to about 27 to 34 mmHg, producing a gradient to facilitate placental excretion of fetal CO_2. Permissive hypercapnia has not been evaluated in pregnancy, and maternal hypercapnia could produce fetal respiratory acidosis. This acidosis likely does not have the same ominous implications for the fetus as the lactic acidosis produced by hypoxemia, which implies significant tissue hypoxemia[56,57].

Hypocapnia caused a lower Apgar score and delayed neonatal breathing. Another small study compared ventilated women delivered with mild hypercapnia (mean CO_2: 57.6 mmHg) with ventilated women with mild hypocapnia (mean CO_2: 26.4 mmHg) and women managed with a local anesthesia block (mean CO_2: 30.1 mmHg). The hypercapnic group had a statistically significantly higher Apgar score at delivery. If necessary, mild hypercapnia with $PaCO_2$ maintained less than 60 mmHg has been recommended for pregnancy[56]. It should be noted that the right shift of the hemoglobin oxygen dissociation curve caused by acidosis may negate the beneficial oxygen-carrying characteristics of fetal hemoglobin[58].

It has been suggested that delivery of the pregnant patient with respiratory failure will result in the improvement in the mother's condition. However, a significant benefit to the mother has not been consistently demonstrated. If the fetus is at a viable gestation and is at risk due to intractable maternal hypoxia, there may be a benefit to the fetus in delivery. The delivery should not be performed solely in an attempt to improve maternal oxygenation or ventilation. It is essential that the ICU have prearranged plans for urgent delivery and neonatal resuscitation in the event of spontaneous labor or sudden maternal or fetal deterioration. This should include the immediate availability of all the necessary equipment, drugs and staff contact details[59].

Conclusions

Pregnancy modifies pulmonary function and the natural history of common lung pathologies. Women with respiratory problems are a challenge and the condition of the fetus must always be kept in clinical judgment.

The attitude in pregnancy depends on the mother's respiratory compensatory state, with postpartum decompensation, whose severity necessarily implies an interdisciplinary pneumology-obstetrician collaboration.

A major decision facing this multidisciplinary team is the potential benefit of delivery for the mother – this cannot always be predicted, and the decision should be based on the overall risk balance to both mother and fetus. ■

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