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Review

Pulmonary Disease during Pregnancy

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Abstract

Asthma and, in a smaller frequency, pneumonia are the most common pulmonary diseases associated with pregnancy. Tuberculosis is quite rare at pregnant women. The diagnosis of these pulmonary diseases during pregnancy is not always easy. The normal biological changes that take place while childbearing make the diagnosis difficult to achieve. Medical history, clinical findings and specialized case specific paraclinical examination contribute decisively to the diagnostic approach of pulmonary diseases upon pregnant women. In the current article, based on the systematic citation of the modern literature references, a brief review of asthma, pneumonia and tuberculosis during pregnancy is attempted, mostly related to the current diagnostic approach, the proper knowledge of which is able to ensure the utmost possible prognostic outcome for both the mother and the embryo – newborn.

Keywords: Asthma, Pneumonia, Tuberculosis, Diagnosis, Pregnancy.

INTRODUCTION

In general, it is known that during pregnancy a series of normal biochemical and anatomical changes take place, in both systematic and regional level. The normal adaptation in pregnancy includes a group of changes mainly regarding the circulatory, the hormonal and the immunobiological system, that aim to the insurance of a stable and ideal environment for the growth of the embryo, while at the same time effectively ensures the mother's well – being. In addition, during pregnancy, a series of biochemical and mechanical changes take place that affect the function of the respiratory system and present themselves with the symptom of dyspnea. Knowing the changes that take place in the pulmonary function in both normal pregnancies and the pregnancies where a pulmonary disease if affecting mother's lungs is of high importance, because the pathological function of the respiratory system is possible to result in serious problems concerning the progression of the pregnancy and the labor.

Asthma during Pregnancy

Asthma is a chronic inflammatory disease of the bronchi that is able to provoke a disseminated, of any degree, obstruction of both the major and the minor pulmonary routes. Asthma is the most common pathological status of the respiratory system that affects pregnancy and is connected with a broad spectrum of adverse maternal and perinatal outcomes (Zanforlin et al, 2016). The frequency of appearance of asthma during pregnant women is elevated over the last years. Thus, while its possibility of appearance which was estimated at the end of the 90s decade was 1% (Schatz et al, 1988), based on the current literature data, the frequency of asthma occurring during pregnancy is estimated to be 4%-8% of the total number of pregnancies (Dombrowski, 2006; Racusin et al, 2013). Recently, Kelly and his research team, while analyzing the results of their research, resulted that asthma is a common and sometimes

Table 1. Clinical manifestation of asthma during pregnancy

• coughing
• nasal discharge
• nasal congestion
• constrictive chest pain
• dyspnea
• paroxysmal coughing
• viscous expectoration
• expiratory wheezing
• exhalation delay
• disseminated dry rattle sound
• dilation of the intercostal spaces
• chest in drawing
• contraction of cervix muscles

serious pathological entity that affects around 8% of the total number of pregnant women (Kelly et al, 2015). Nevertheless, asthma attacks are not common during pregnancy. Based on older data, it's estimated that one out of 4000 pregnant women will have an asthma attack during her pregnancy (Hernadez et al., 1980).

However, based on current research data, it's estimated that 1/3 of asthmatic pregnant women present an aggravation of their disease that can develop to critical asthma syndrome, that includes status asthmaticus and near – fatal asthma (Chan et al, 2015). Recently, Gade et al. published that negative consequences of asthma concerning fertility are dependent on the mother's age and the stage of the disease, thus suggesting that the systematic disease with systematic inflammation might relate to reproductive procedures (Gade et al, 2014). There are many studies that demonstrate that asthma exacerbation during pregnancy increase the risk of proeclampsia, gestational diabetes, placenta previa, placenta abruption, intra – uterine growth restriction of the fetus and premature labor. In addition, these women present a higher risk of bleeding during labor, an increased frequency of cesarean sections, a higher risk of pulmonary embolism and a high risk and admission of the patient in an Intensive Care Unit (Ali et al., 2016; Namazy and Schatz, 2018).

Asthma diagnosis during pregnancy

Diagnosis of asthma during pregnancy is usually not easy. Mild clinical manifestations of the disease which are possibly similar to the normal pregnancy symptoms delay the timely and accurate diagnosis. Clinical symptoms of asthma during pregnancy don't usually differ from those observed on non-pregnant patients (Apter, 2010), as demonstrated on the table above (Table 1). Symptoms of the disease usually appear progressively, within hours or days after the contact with the provoking factor. Most commonly they appear collocated with symptoms of the upper respiratory system, like sneezing, nasal discharge and nasal congestion. The exacerbations usually occur during night hours. Typical symptoms of asthma attack include constrictive chest pain, dyspnea, expiratory wheezing, paroxysmal coughing and viscous expectoration. The gravity of the symptoms vary greatly among patients, even between crises on the same patient. It ranges from paroxysmal dry coughing, especially during the early morning, to intense dyspnea with labored breathing and cyanosis. Findings from clinical examination vary greatly, depending on the gravity of the exacerbation. In its typical form, the findings during the auscultation of the respiratory system are expiratory wheezing, delayed exhalation and disseminated dry rattle sound. The patient usually is in a mandatory seated position and presents tachypnea, dilation of the intercostal spaces, chest indrawing and contraction of the cervix muscles, because of the labored breathing (Brand, 2013; Patadia et al, 2014; Brand et al., 2015).

In general asthma diagnosis during pregnancy is based on medical history, which should be detailed in every pregnant woman presenting coughing and dyspnea, on the characteristic clinical findings and on the laboratory and imaging investigations. Laboratory blood testing during a paroxysmal asthma attack usually doesn't reveal pathological findings and is mainly useful in excluding other conditions or in determining the concurrent existence of another pathological entity. Diagnostic approach of pregnant women with asthma should overcome the traditional hesitation of imaging during pregnancy. In the cases when a clinical doctor considers that performing projection radiography is essential, pregnancy should not be a contraindicating factor. Performing chest X-ray on a pregnant woman should be done with the use of a special radiography apron protecting the abdomen. It is estimated that the radiation dosage that the fetus receives during a postero – anterior X – ray is approximately 100 times smaller than the radiation the mother receives (Goodnight and Soper,

2005). Even so, chest X-ray doesn't confirm the diagnosis, but contributes significantly to the differential diagnosis of the disease and to the exclusion of other pulmonary diseases with similar symptomatology. Arterial blood gas analysis during the acute phase of the disease contributes to the determination of the asthma's severity. High levels of immunoglobulin E (IgE) indicate in general predisposition of the patient towards this condition. Detection of specialized immunoglobulin in blood (RAST test) is possible to demonstrate sensitivity against certain allergens. This kind of allergen sensitivity can be discovered also by allergy skin testing, during which a small dose of allergen is administrated cutaneously and afterwards the topical effect is interpreted (Guideline, 2007). The determination of the levels of Nitric Oxide (FeNO), which in normal pregnancy are within normal levels, is an important examination in the diagnosis of asthma during pregnancy, since these levels are found increased on asthmatic pregnant women (Wu et al, 2015). The examination of the respiratory function through spirometry is the most crucial element in the investigation and determination of the severity of asthma, establishing at the same time the confirmation of the diagnosis. During the exacerbation of the disease, the forced expiratory volume in 1 second (FEV1) and the peak expiratory flow rate (PEFR) are both decreased. The noted decrease of the above markers is proportionate to the severity of the bronchial obstruction. When the asthmatic patient is not experiencing an asthma attack, spirometry can be normal or can indicate a decrease of air flow on small airways through the estimation of peak expiratory flow (PEF) (Yawn, 2008; Bealert and Greenberger, 2012).

Finally, regardless of the etiological inductive factor of asthma during pregnancy, in any case, especially when the disease is not presenting itself with its typical symptomatology, apart from normal pregnancy dyspnea (Bidad et al, 2010) differential diagnosis should include pathological conditions, such as gastroesophageal reflux disease, pneumonia, pulmonary embolism, pulmonary edema and chronic obstructive pulmonary disease, the differential diagnosis of which requires special attention (Bateman et al, 2009; Simons and Schatz, 2012). Chronic obstructive pulmonary disease (COPD) is characterized by obstruction of bronchi which is not completely reversible, like it happens in asthma. Usually it is a disease that progressively deteriorates and is related directly and almost exclusively with smoking. Nevertheless, it is possible that asthma and COPD coexist in some patients (Murray, 2010)

Pneumonia during Pregnancy

Pneumonia is the pathological condition that is characterized by an acute inflammation of the lung parenchyma. Pneumonia is not common during pregnancy. The frequency of pneumonia among pregnant women is estimated to be equivalent to the frequency of pneumonia incident on non-pregnant women (Cheung et al, 2011). In general, it is estimated to affect 0.78 to 2.7 cases in every 1000 pregnancies, and is one of the most common pregnancy-related causes of death (Berkowitz and LaSala, 1990). During most recent years, a decrease is noted in the frequency of pneumonia incidence. Thus, from 6.3 to 8.5 out of 1000 pregnancies that was the incidence estimation before 1965 (Hopwood, 1965), recently Sheffield and Cunningham concluded by analyzing the data of their research that the frequency of pneumonia occurrence during pregnancy is 0.5 to 1.5 out of 1000 pregnancies (Sheffield and Cunningham, 2009). Pneumonia is more common during the last trimester of pregnancy. The occurrence frequency of pneumonia during the first trimester is small and is estimated to constitute 0% - 16% of the total number of cases (Madinger et al., 1989).

Diagnosis of pneumonia during pregnancy

The diagnosis of pneumonia during pregnancy is not usually easy. The clinical manifestations of pneumonia during pregnancy don't diverge greatly from those that are presented in non-pregnant patients, as shown on the table below (Table 2). The main symptoms of pneumonia are fever with shivering, coughing, pleuritic chest pain and dyspnea, and they are present in the majority of the cases. Usually they are accompanied with other non-respiratory symptomps, such as malaise, nausea, headache and muscle ache. Munn and his team demonstrated by analyzing the results of their research that out of the total number of pneumonia incidents during pregnancy, approximately 2/3 (a percentage of 59.3%) presented productive coughing, 32.2% presented dyspnea and 27.1% were experiencing pleuritic chest pain (Munn et al, 1999). Even though it is known that the clinical examination on pregnant women with pneumonia has low sensitivity and specificity, clinical findings such as decreased breath sound, wheezing, crackling sound or acoustic bluntness may contribute to the diagnosis of the disease (Kasper et al., 2005).

In general, diagnosis of pneumonia during pregnancy is based on medical history, on specific clinical findings and on laboratory -imaging investigations. Laboratory examination on pregnant women suspected of having pneumonia should include a complete hematological and biochemical examination to determine the levels of blood glucose and estimate liver and renal function. Blood culture is necessary for isolating the cause of the disease (Guidelines, 2001). However, blood cultures on patients with pneumonia during pregnancy are rarely found positive (Panting – Kemp et al, 2000; Yost et al., 2000).

Diagnostic approach of pneumonia during pregnancy should not be limited by the "traditional" hesitations of

Table 2. Clinical manifestation of pneumonia during pregnancy

• fever
• shivering
• coughing
• pleuritic chest pain
• dyspnea
• malaise
• nausea
• headache
• muscle aches
• decreased breath sound
• wheezing
• crackling sound
• acoustic bluntness

performing imaging investigation on pregnant women, as stated above. Chest X-ray is necessary for the confirmation of the diagnosis. Romanyuk and his team concluded by analyzing the results of a recent study that the most common site of installation of pneumonia is the left lower lobe (53.4% of the cases), followed by the right lower lobe (26.3% of the cases) and the right middle lobe (8.3%). Also, they concluded that in 9.8% of the cases pneumonia is associated with pleural effusion (Romanyuk et al, 2011). In the case of pneumonia caused by varicella zoster virus (VZV), the chest X-ray usually demonstrates a typical median tuberous archetype (Ground-glass opacification) or areal infiltration, confirming the diagnosis, in combination with a positive history of recent viral infection by VZV and the typical rash and fever symptomatology (Pastuszak et al., 1994).

Finally, apart from the causal factor responsible for pneumonia incidence during pregnancy, in any case, especially in cases when the disease is not presented with its typical symptomatology, differential diagnosis should include pathological conditions such as drug-induced pneumonitis (nitrofurantoin), bronchial asthma, pulmonary embolism, amniotic fluid embolism, vascular air embolism and pulmonary edema, caused by hypertension or after the use of tocolytic drugs, in the attempt to suspend preterm labor (Shariatzadeh and Marrie, 2006).

Pulmonary Tuberculosis during Pregnancy

Pulmonary tuberculosis is a pathological condition characterized by an acute inflammation of the lung parenchyma, which is caused by mycobacterium tuberculosis, an immobile, acid-resistant, curved rod-shaped, aerobic bacterium. Tuberculosis is not common during pregnancy. Pregnancy is not a risk factor that favors the manifestation of pulmonary tuberculosis. In addition, the frequency of incidence of extra-pulmonary tuberculosis on pregnant women is estimated not to differ significantly from the related frequency on non-pregnant women (Ormerod, 2001). According to the World Health Organization the frequency of tuberculosis incidence has been increased over the last years. Specifically, out of 6.6 million cases that were reported at 1990, the total number of patients with tuberculosis at 2008 is estimated to be 9.4 million, while 3.6 million of new cases are women (WHO, 2009). More recently, World Health Organization published that the year 2013 there were 3.3 million cases of women with tuberculosis and 510000 deaths. Also, it is estimated that 1/3 of those women were infected by the Human Immunodeficiency Virus (HIV) (WHO, 2014).

In general, tuberculosis is a significant cause of death in women today. It is estimated that tuberculosis is responsible for 700000 deaths per year. It is a major non-obstetric cause of maternal mortality. The estimations indicate that 1/3 of the deaths are due to tuberculosis in women that were infected during childhood and in the majority of the cases it refers to the developing countries (Grange et al, 2010). Kothari and his team, after analyzing the data of their multi-year research in London, discovered an increase in thetuberculosis incidence during pregnancy (Kothari et al, 2006). More recently, Knight and his research team published that the incidence of tuberculosis during pregnancy in the United Kingdom was 4.2 cases in every 100000 pregnancies, or approximately one case every 24000 pregnancies (Knight et al, 2009). Recently, Mathad and Gupta concluded that the frequency of active tuberculosis on pregnant women in developed (low risk) countries is 0.06%-0.25%. In developing countries the frequency fluctuates between 0.07% and 0.5% in HIV negative women, while in HIV positive women the frequency of tuberculosis is increased and isfrom 0.7% to 11% (Mathad and Gupta, 2012). In more recent years, in 2014, Sugarman and his team, after analyzing their epidemiological research, presented 216500 cases of active tuberculosis during pregnancy. Also, the same research team published that 41.3% of the cases were patients from the African

Table 3. Clinical manifestation of tuberculosis during pregnancy

• persistent coughing
• fever
• sweating
• loss of appetite
• weight loss
• indisposition
• malaise
• haemoptysis
• dyspnea
• chest pain
• respiratory failure
• non-specific clinical findings

continent (Sugarman et al, 2014).

Diagnosis of pulmonary tuberculosis during pregnancy

The diagnosis of tuberculosis during pregnancy is not usually easy. Clinical manifestation of tuberculosis in pregnancy doesn't differ from the symptomatology present on nonpregnant patients (Getahun et al, 2012), as displayed in the table below (Table 3). Tuberculosis is in general a quiet disease. It manifests with symptoms and clinical findings that are minor or absent even in progressed stages of the disease. In pulmonary tuberculosis the main symptoms are coughing, fever, sweating, loss of appetite, loss of body weight and malaise. Persistent coughing, which could be productive or dry, is the most common symptom. Haemoptysis usually appears during late stages of the disease. Coughing, which is the most sensitive indicator of active tuberculosis is described in 40%-80% of patients with pulmonary tuberculosis, while fever and weight loss are present in less than half the cases. Haemoptysis is present in less than a quarter of the patients. Dyspnea is mostly related with pleural effusion, but in the extended parenchymal disease or in military tuberculosis a serious respiratory failure can occur. Chest pain often indicates pleura or underlying parenchyma involvement. Clinical examination findings are neither specific nor sensitive in diagnosis of pulmonary tuberculosis during pregnancy (Samb et al, 1997; Catanzaro et al, 2000; Nhan – Chang and Jones, 2010; Nguyen et al, 2014).

In general differential diagnosis of pulmonary tuberculosis on pregnant women is based on medical history, specific clinical findings and laboratory – imaging investigation. The purpose in taking medical history and performing clinical examination is to be able to recognize people of high risk that should be specifically examined for tuberculosis. Risk factors are of important significance in the diagnostic procedure. Because of the aerogenous transmission of tuberculosis, every person that is in close contact with the patient is in possible risk of infection. Socioeconomic factors related to tuberculosis are ethnic minorities, immigration to countries with high tuberculosis incidence, low income, homelessness, living in overcrowded housing and professional exposure (Cantwell et al, 1994; lademarco and Castro, 2003; Jagielski et al, 2010). Routine laboratory tests don't contribute significantly to the diagnosis of the disease. Usually they don't show any abnormalities, except for late stages of the disease. Most common laboratory findings are anemia and leukocytosis. There have also been described cases of tuberculosis presenting hyponatremia and hypocalcemia (MacGregor, 1975; Lind and Ljunghall, 1990).

Tuberculin sensitivity test is considered safe to be performed in pregnancy. Diagnostic value of the test in detecting underlying infection is not affected by pregnancy. A positive skin reaction after performing a tuberculin sensitivity test is diagnostic of past infection. In total 75% - 90% of patients with active tuberculosis react to the cutaneous injection of tuberculin. In addition, false positive results can emerge, due to improper administration of evaluation of the skin reaction, past vaccination of bacillus Calmette – Guerin (BCG) and past infection from another mycobacterium (Baquero – Artigao et al, 2015).

Chest X-ray in primary infection is usually normal. Alternatively, the disease can be presented with a form of non-specific pneumonitis, which is difficult to differentiate from bacterial pneumonia or periportal or paratracheal lymphadenopathy. Exacerbation of tuberculosis is typically presented as an infiltration in the upper or posterior part of upper lobes. This infiltration can be presented as an effusive mass or a fibrous lesion, and in 80% of the cases it has both elements. Cavitational formation is present in 50% of the cases and the fibrosis with volume decrease in 30% of the patients (Mc Adams et al, 1995; Andreu et al, 2004; Sheriff et al, 2010).

In cases with high suspicion of pulmonary tuberculosis based on clinical and imaging results, the proper following step in order to achieve a diagnosis is sputum

examination. At least three samples of morning sputum should be sent to the laboratory to be examined and cultured. Direct microscopic examination for mycobacterium tuberculosis is a simple, low cost and fast procedure. However, microscopic observation is incapable of differentiating between mycobacterium tuberculosis and atypical mycobacteria. Sputum culture has higher sensitivity and specificity in diagnosing tuberculosis compared to sputum smear microscopy. Sensitivity of culture is higher than 80%, if tuberculosis infection is considered the final clinical diagnosis. Major disadvantage in sputum culture is the prolonged time period until the results are available (Yajko et al, 1994).

Finally, pregnant women with tuberculosis should be checked for HIV infection, because there is a high probability of extrapulmonary or multidrug-resistant tuberculosis in this group of patients. HIV infection is a significant risk factor that can convert latent tuberculosis to an active state of the disease. Tuberculosis development during pregnancy or in the postpartum period in a patient infected with HIV is related to a significant increase of mortality for both the mother and the embryo – neonate (Gupta et al, 2007; Gupta et al, 2011).

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