Two Successful Pregnancies in a Patient With Advanced Liver Cirrhosis and Hepatopulmonary Syndrome

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Hepatopulmonary syndrome (HPS) is characterized by the presence of chronic liver disease, intrapulmonary vascular dilatation, and arterial hypoxemia.[1] The pathophysiology of the pulmonary features involve ventilation-perfusion mismatch, oxygen diffusion limitation, and varying degrees of intrapulmonary shunting. The natural history of HPS is poorly understood to date, and significant mortality, despite therapeutic attempts to correct hypoxemia, has been reported.[1] The role of liver transplantation in this condition and the timing of transplantation is still controversial. Nevertheless, the progressive worsening of hypoxemia, irrespective of Child-Pugh class, may be considered an indication for liver transplantation.[2,3]

Pregnancy in patients with liver cirrhosis is not common. There is significant perinatal mortality, and the effect of pregnancy on the underlying liver disease remains uncertain. Pregnancy in a patient with lung disease, however, is known to have an adverse effect on both the woman and the fetus. In this case report, we describe the successful completion of 2 pregnancies in a woman with autoimmune type I hepatitis and Child-Pugh class B cirrhosis complicated by HPS.

Case Report

A 31-year-old woman with a 20-year history of type I autoimmune hepatitis was receiving follow-up treatment in our liver clinic. Ten years earlier, deterioration in her nutritional state and synthetic liver function confirmed liver cirrhosis. Simultaneously, she developed progressive exertional dyspnea. Pulmonary function tests showed restrictive lung disease and carbon monoxide transfer factor (TLCO) of 45% of the predicted value, whereas chest radiograph and lung scan were normal. Contrast echocardiograph displayed normal two-dimensional echo study and contrast right-to-left shunt at the pulmonary level. Oxygen saturation at rest was 94% but dropped to 84% at minimal effort. These findings confirmed the diagnosis of HPS.

The patient's respiratory condition had been stable for 2 years when she began to complain of worsening dyspnea. At that time, physical examination revealed a well-oriented, dyspneic patient (24–26 respirations/min, with oxygen saturation at 82–83% after minimal exertion), without peripheral signs of chronic liver disease. The patient's lungs were clear, and her spleen was palpable 6 cm below the costal margin. The rest of the physical examination was unremarkable. Laboratory tests revealed the following: total protein 8.2 g/dL, albumin 2.9 g/dL, international normalized ratio 1.6–1.7, total bilirubin 1 mg/dL, and direct bilirubin 0.6 mg/dL. Transaminases were normal, and hemoglobin measured 9.8 g/dL, white blood cell count 3,520 cells/mL, and platelet count 67,000/mL. According to these parameters, her Child-Pugh score was defined as B. Repeated pulmonary function tests showed a restrictive pattern with an obstructive component (high residual volume with 111% of predictive value), without deterioration in diffusion capacity. The patient started treatment with inhaled bronchodilator and showed mild improvement.

Approximately 1 year later, the patient became pregnant. A team consisting of a hepatologist, pulmonologist,

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and gynecologist was created for the close monitoring of the pregnancy. The patient was placed on continuous oxygen inhalation to avoid simultaneous maternal and fetal hypoxemia. TLCO and oxygen saturation were stable during pregnancy, and overall the pregnancy was uncomplicated. At 37 weeks, the patient gave birth by cesarean section to a healthy baby girl weighing approximately 7 pounds.

Early postpartum course was unremarkable. The patient continued usual follow-up treatment in the outpatient liver clinic, and her liver function tests did not change.

Two years later, the patient became pregnant again. At the beginning of this pregnancy, she continued her usual medications, prednisone 5 mg daily and propranolol 30 mg daily. Pulmonary evaluation parameters remained stable, and oxygen saturation was 98%, with continuous oxygen. At Week 32 of the pregnancy, echocardiograph revealed normal left and right ventricle systolic functions and, for the first time, mild pulmonary hypertension with an estimated pulmonary artery pressure of 45 mm Hg was discovered. The patient delivered a healthy baby boy by cesarean section 4 weeks later.

Discussion

This patient had liver cirrhosis due to type I autoimmune hepatitis, complicated by HPS, but still had 2 successful pregnancies. It has long been believed that women with autoimmune hepatitis have difficulties conceiving and maintaining pregnancies.[4] Although favorable outcomes have been reported in several cases,[5] amenorrhea and anovulation are common in women with established cirrhosis, and pregnancy is considered to be relatively rare.[6] Decreased fertility in women with advanced liver disease may provide a degree of “natural” protection for patients who would have increased risk if they did become pregnant.[7]

This patient has HPS, a rare complication of cirrhosis that occurs in 1.5–4% of patients.[1] The critical event in the pathogenesis of HPS is vasodilatation and the creation of arteriovenous (AV) malformation in lung vasculature. Increased pulmonary exhaled nitric oxide (eNO) may contribute to the development of HPS as part of general vasodilatation occurring in liver cirrhosis.[8]

Pregnancy may cause a further increase in pulmonary shunting, with the development of high-output congestive heart failure, as well as sodium and water retention.[9] There is growing evidence that estrogen upregulates eNO synthesis in sinusoidal endothelial cells via estrogen receptor–dependent mechanisms, possibly contributing to vasodilatation.[10] On the other hand, eNO may be involved in endometrial functions, such as endometrial receptivity, implantation, and menstruation, which could have improved the chances of pregnancy in our patient.[11]

In light of the considerations mentioned above, we expected to observe an overall worsening of our patient’s respiratory condition, especially during the second and third trimesters of her second pregnancy. A recent paper describing the appearance of HPS during pregnancy in otherwise asymptomatic cirrhotic patients supports this expectation.[12] Surprisingly, the parameters of respiratory function tests and oxygen saturation in our patient did not show any significant changes compared to those during the first pregnancy.

There are two possible explanations for her relatively stable condition during the first pregnancy and the small improvement of respiratory functions during the course of the second pregnancy. One is a mechanical explanation. It is well known that pregnant women breathe using the middle and upper lobes of their lungs. The raised diaphragm pressure on the bases of the lungs, where AV malformations usually occur, may limit the shunt area. The second explanation is related to estrogen. Estrogen or estrogen-progesterone therapy has been reported to be useful in the treatment of chronic bleeding caused by gastric antral vascular ectasia (GAVE).[13] The mechanisms by which estrogen might alter the bleeding patterns of affected patients are unknown, but possible explanations include stasis in the microcirculation and augmentation in the integrity of the vascular endothelium.[14] If the mechanisms of the development of GAVE in gastric mucosa and the mechanisms of AV malformations in lung vasculature in cirrhotic patients are similar, it is possible to conclude that estrogen may decrease the severity of HPS.

We speculate that the positive impacts of breathing mechanics and estrogen on AV malformations can neutralize the negative influence of increased eNO concentration, vasodilatation, and shunting. The finding of mild transient pulmonary hypertension on echocardiography also helps to explain the lack of deterioration during both pregnancies of our patient.

In addition, there is growing evidence that HPS can show spontaneous resolution. The proposed mechanism of this phenomenon is portopulmonary hypertension overlap, which may inhibit the influence of HPS.[15] It has been speculated that both endothelin-1 and eNO may be involved in this intriguing mechanism.[15]

In conclusion, pregnancy, although uncommon, may occur even in advanced liver disease with rare complications such as HPS. If the decision to continue the pregnancy is made, tight multidisciplinary monitoring with close collaboration among pulmonologists, hepatologists, and obstetricians is warranted. Researchers also need to pursue further the investigation on the possible influence of estrogen on HPS’s severity, as well as the mechanisms of HPS and portopulmonary hypertension overlap.

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Review

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The case study by Veitsman and colleagues describes two successful pregnancies in a patient with autoimmune hepatitis and hepatopulmonary syndrome (HPS).[1] Autoimmune hepatitis is a rare condition, and successful pregnancy has been reported in only a small number of cases in which disease activity is under control. Morbidity in the setting of autoimmune hepatitis and pregnancy is associated with prepartum flares at a rate of 21–47% and postpartum flares at a rate of 12–52%, typically in the first 3 months following delivery.[2] The most common adverse event associated with fetal mortality in pregnant autoimmune hepatitis patients is premature delivery, which is reported in up to 17% of cases.[3-4] Management of patients with autoimmune hepatitis-related cirrhosis who become pregnant is simple in theory; however, it involves the development of trust between doctor and patient, as well as compliance and frequent visits to a multidisciplinary care team for regular monitoring. The continuation of regular immunosuppression, typically azathioprine, does not carry an increased teratogenic risk, although breastfeeding is usually not advised due to the theoretical risks of breast milk carriage and bone marrow suppression in newborns.

The case by Veitsman and associates is noteworthy for many reasons. First, it highlights the fact that patients with stable autoimmune hepatitis-related cirrhosis may be capable of successful conception and completion of pregnancy. Second, it confirms that the continuation of standard immunosuppression, rather than an escalation in therapy, is generally sufficient to control disease activity. Throughout both pregnancies, the patient's disease was apparently stable, and with a total follow-up of 3 years so far, she has suffered no prepartum or postpartum complications in disease activity.

There is a close, recognized association between liver disease and the development of respiratory symptoms. In one reported series, over 50% of patients with cirrhosis complained of breathlessness.[5] This respiratory symptom can often be explained by the physiologic changes

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that develop in patients with cirrhosis including poor thoraco-abdominal compliance, diaphragmatic splinting in the setting of ascites, muscle weakness, previously undiagnosed lung or cardiac disease, and the development of pulmonary arteriovenous abnormalities and exertion-related dyspnea. Physical examination often provides clues to possible underlying respiratory abnormalities. The presence of large-volume, tense ascites, poor nutrition, muscle wasting, spider angioma, finger clubbing, and cyanosis are easily recognizable. The impairment of arterial oxygenation due to pulmonary vascular abnormalities and the association of chronic liver disease form the increasingly recognized triad of symptoms of HPS. The classic definition of HPS describes an elevated age-adjusted alveolar-arterial oxygen gradient ($AaPO_2$) in room air (>15 mm Hg or >20 mm Hg in patients >64 years of age), with or without hypoxemia, resulting from intrapulmonary vasodilatation in the presence of hepatic dysfunction or portal hypertension.[6] The previous exclusion of coexisting cardiovascular and respiratory disorders is no longer necessary, as HPS has been seen alongside these conditions.[7] It is these conditions that may provide a reversible element in HPS management. $AaPO_2$ varies with age, even in normal individuals; therefore, it is important to use age-adjusted levels.

Alveolar-arterial oxygen abnormalities are paramount in the diagnosis of HPS, as hypoxemia in itself is not required. The presence of resting hypoxia may provide a clue, if only for further evaluation and exclusion of a potential diagnosis. Routine assessment of patients with hypoxia includes chest radiograph and pulmonary function tests alongside arterial blood analysis. Measurement of peripheral oxygen saturations provides a cheap and simple outpatient screening tool rather than a diagnostic test. Measurement of arterial oxygen concentrations in room air by blood gas analysis is the gold standard of diagnosis and is necessary to establish the severity of disease.

The development of HPS is thought to result from local endothelial nitric oxide and carbon monoxide release, which leads to vascular dilatation and pulmonary diffusion-perfusion mismatch (arterial-alveolar gradient). Pulmonary vascular abnormalities can be determined either by transthoracic contrast bubble echocardiograph or macro-aggregated albumin lung scanning. The presence of contrast or bubbles in the left ventricle after 3 beats is a classic sign of shunting on a pulmonary level and is hence diagnostic of HPS.

The prevalence of HPS has been reported as ranging from 1.5% to 24% of cirrhotic patients but recently has also been found in certain noncirrhotic states.[8] The severity of underlying liver disease does not appear to influence the development of HPS, although there is a correlation between hypoxemia and Child-Pugh class. The cause of death in patients with HPS appears to result from portal hypertension or hepatic dysfunction and is not associated with hypoxia. However, HPS appears to influence the progression of liver disease and complications associated with portal hypertension, and is an independent predictor of survival.[9] This association also affects patient survival, as the 5-year median survival rate is only 23% in patients with HPS compared with 63% in cirrhotic controls without HPS.[10] Because of the close association of chronic liver disease and HPS, there is only one recognized definitive treatment: liver transplantation (LT). LT can result in total resolution or significant improvement in gas exchange in more than 85% of patients transplanted for HPS, although normalization may extend beyond 12 months.[6]

The diagnosis of HPS carries significant morbidity and mortality. The severity of underlying liver disease itself may not warrant consideration for transplantation, but when combined with HPS, the associated mortality is significant enough to consider LT. Indeed, prioritization for transplantation is widely accepted for HPS cases with significant hypoxemia. The 5-year transplant survival rate in patients with HPS (including severe HPS) who undergo transplantation is equal to the survival rate of patients without HPS.[7] Therefore, liver transplantation is the only available therapeutic intervention that appears to influence long-term mortality. This appears to hold even for patients with severe hypoxemia. Patients previously excluded from transplantation would therefore benefit, even though recent evidence suggests that postoperative mortality is higher in the first 3 months following transplant in this group.[10] A classification system for HPS based on arterial oxygen tension (PaO_2) has been proposed: PaO_2 less than 50 mm Hg indicates very severe HPS and is excluded from transplantation; PaO_2 between 50–60 mm Hg indicates severe HPS; and PaO_2 between 60–80 mm Hg indicates moderate HPS.

Consideration for LT in this patient would solely be due to the diagnosis and severity of HPS, rather than to underlying liver disease. The difficulty is in establishing the diagnosis and then stratifying severity from the available data. Resting or baseline PaO_2 is crucial and would provide an important marker of disease severity. HPS may indeed be an indication for LT, but the determination of severity allows for informed consent and assessment of postoperative mortality. This would be significant if the O_2 saturations of 84% did not improve postpartum. The presence of pulmonary shunts diagnosed on transthoracic contrast echocardiograph is a classic sign for HPS, but formal assessment of the arterial-alveolar gradient should have been undertaken prior to pregnancy. Current PaO_2 measurements would be extrapolated from documented arterial saturations, rather than direct PaO_2 measurements. Arterial saturations ranged from 84% to 94% in this patient, approximating PaO_2 to between 55 and 80 mm Hg. These extremes would stratify HPS between severe and moderate. Transient changes in physiology may be important in this case and may need to be taken into consideration, as improvement postpartum is normally likely to occur.

The physiologic changes that occur in pregnancy are also well recognized. The systemic vasodilatation that occurs in the first trimester may exacerbate pulmonary vascular abnormalities and increase pulmonary shunting. This would worsen hypoxia, albeit only transiently, placing greater strain on the right side of the heart. It is unsurprising in this case that arterial saturations were seen to deteriorate during this time period. Changes after the first trimester are associated with the pooling of blood, with decreased venous return being the main cause of hemodynamic compromise. Thus, pulmonary shunting would theoretically improve in the later stages of pregnancy. There are no reported cases in the literature describing the development of spontaneous pulmonary vascular abnormalities occurring as a direct result of pregnancy.

The use of supplemental oxygen in patients with severe HPS or exertion-induced hypoxemia is well recognized. Data are somewhat limited regarding efficacy or the relationship to reduction in morbidity, although improvements in exercise tolerance and quality of life may justify the use of supplemental oxygen. The presence of a reduced diffusion capacity of carbon monoxide is recognized in HPS but also in other conditions such as pneumonitis, interstitial lung disease, and anemia. The presence of underlying lung disease or anemia would explain the relative hypoxia and also the lack of progression over the documented 3-year period.

In view of both the development and progression of symptoms, it is critical to reassess this case further. It would thus be appropriate to repeat baseline investigations and to determine the possibility of underlying lung disease in addition to establishing a resting PaO_2 value. The development of pulmonary hypertension further clouds the diagnosis. Indeed, there appears to be increasing recognition of the overlap of these conditions, even extending into the posttransplant period. A recent case report described the possible overlap between HPS and portopulmonary hypertension (PPHTN) in one patient,[11] and in our own practice, we have identified a handful of cases with apparent overlap between these entities.

PPHTN is characterized by pulmonary vasoconstriction through vasoactive mediators, the most important of which is endothelin-1, resulting in pulmonary hypertension. The development of PPHTN does not exclude candidates from transplantation with mild or moderate disease, but consideration for transplantation should be undertaken as soon as possible because coexistent disease and right ventricular dysfunction would render the likelihood of survival to be low. A possible hypothesis is that the development of PPHTN in the setting of HPS or indeed interstitial lung disease provides transient improvement in gas exchange and symptoms, but would eventually lead to pulmonary hypertension and right-sided heart failure.

In conclusion, although HPS is an indication for transplantation independent of the severity of liver disease, there should be investigations that include arterial blood gas analysis and transthoracic contrast echocardiograph. Although early posttransplant survival depends on the severity of disease, the 5-year survival rate for HPS patients equals that of patients without HPS. The clinical entities of HPS and PPHTN may in fact represent extremes of a spectrum in respiratory complications associated with liver disease.

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