

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Autoimmune Hepatitis in Pregnant Women



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G&H What is autoimmune hepatitis, and how common is it in the general population?

MP Autoimmune hepatitis (AIH) is an autoimmune disease of the liver whose cause is unknown. AIH is more common in women than in men (by approximately 8:1) and is seen in 10 to 20 per 100,000 people in the general population. It is associated with other autoimmune diseases, especially thyroid disease. AIH was initially thought to present mainly in young and middle-aged women, but it is now clear that the first episode can occur at any age, even in people in their 80s.

G&H Is the rate of pregnancy increasing in women who have AIH?

MP The rate has probably increased since the 1950s and 1960s, when young women with AIH were told not to have children. At that time, some did have children anyway, and it became clear that a successful pregnancy was possible even though there is a higher risk to the fetus and to the mother. However, with excellent control of AIH, this risk is diminished.

G&H How does pregnancy typically affect the disease course of AIH? How common are disease flares during pregnancy?

MP The published literature includes limited numbers of pregnant women with AIH, but up to approximately 20% of patients will flare during pregnancy. Flares are likely increased for a number of reasons. One is that patients

and/or providers may stop medical therapy because they mistakenly think that it is safer for the fetus not to be exposed to medication. In fact, the opposite is true. It is safer for the mother and the fetus if the mother's disease is well controlled during pregnancy.

Another reason for flares is the changing immune status of the mother during pregnancy. Although pregnancy is a relatively immunosuppressed state, the initial onset of AIH can occur during pregnancy, and flares may occur even in well-controlled pregnant women with AIH.

G&H What is the optimal management of AIH during pregnancy?

MP Standard treatment for AIH in general consists of either prednisone or budesonide and azathioprine. All 3 treatments have been shown in randomized, controlled trials of AIH patients in general to prolong life and suppress liver inflammation. Both prednisone and azathioprine use have been reported during pregnancy. Although the studies conducted specifically in pregnant women with AIH have been small, all of them have shown that having well-controlled AIH for at least the year before pregnancy leads to the best fetal and maternal outcomes. Azathioprine and prednisone use in pregnant women did not increase the risk of adverse fetal outcomes, so good AIH control outweighs the risks associated with prednisone or azathioprine during pregnancy. Thus, AIH treatment should be continued during pregnancy.

G&H Are there any scenarios in which treatment should be stopped?

MP I am not aware of any specific scenarios in which treatment should be stopped. The mother should be treated with standard therapy even if AIH presents during pregnancy (which is rare but does occur).

G&H Are there any fetal and maternal risks associated with the current treatment options for pregnant AIH patients?

MP The US Food and Drug Administration states that azathioprine can cause fetal harm when administered to a pregnant woman. Thus, this drug should not be given without weighing the risks and benefits. Azathioprine does cross the placenta, but it has been well studied in solid organ transplant recipients and in patients with ulcerative colitis. Azathioprine therapy has not been shown in those patients to be associated with worse fetal outcomes, although higher preterm delivery rates have been noted. Therefore, women should be aware that there is a small risk with azathioprine therapy, but that risk is smaller than the risk of having a flare and uncontrolled AIH in terms of outcomes to both the mother and the fetus.

As for the other treatment options, there are no data on oral budesonide in pregnancy. In a meta-analysis, prednisone increased the risk of cleft palate after maternal exposure to glucocorticoids in the first trimester (0.2%-0.4%), but no risk was noted in a prospective analysis.

G&H Are there any other treatment options in pregnant patients with AIH?

MP Many physicians have recently started to use mycophenolate mofetil instead of azathioprine to treat AIH, despite the lack of supporting randomized, controlled data. However, this drug is contraindicated in pregnancy because it causes congenital malformation.

G&H If a pregnant patient with AIH does flare, should treatment be increased?

MP Yes. Pregnant patients should be treated exactly the same as nonpregnant patients, which means that flares should be managed with higher doses of prednisone and/or the addition of azathioprine.

G&H How specifically does the presence of AIH affect the course of pregnancy and fetal outcomes?

MP First of all, there is decreased fertility in women with uncontrolled AIH, and they often present with amenorrhea. However, with treatment and, thus, good control

of AIH, fertility improves. Second of all, there are lower favorable fetal outcomes in pregnant women with AIH. Having this disease is associated with lower birth rates, similar to those seen with other autoimmune diseases, and higher premature births. However, there is no increased risk of fetal abnormalities. It is difficult to tell whether there is an effect on first-term abortion rates because many women with AIH have irregular menses, and this issue has not been well studied. There is also a high rate of cesarean section, but it is not clear whether the increase is due to the obstetrician choosing the procedure to lower the risk of peripartum bleeding.

G&H What is the impact of cirrhosis, which is common in AIH, on pregnancy?

MP The impact of cirrhosis on these patients is particularly important. Cirrhosis is found at the first presentation of AIH in up to 40% of patients. Pregnancy in women with AIH and cirrhosis is associated with lower birth rates, and neonates are more likely to be premature.

A large study in California (of over 2 million pregnancies over the past decade) looked at the impact of all-cause cirrhosis (not just cirrhosis associated with AIH) on pregnancy. Thirty-seven women had cirrhosis, and these patients had increased rates of preeclampsia, preterm delivery, low birth weight, and neonatal death. Women who had cirrhosis and portal hypertension had an even higher incidence of all of these outcomes. Small studies of pregnant women with AIH have shown serious maternal adverse events in cirrhotic patients, with death or liver transplant in approximately 10% of women. This is especially important because these patients may seem perfectly healthy and often have compensated cirrhosis prior to pregnancy. Women should be counseled that there is a higher risk of poor fetal and maternal outcomes in pregnant cirrhotic women. These outcomes are not inevitable, but a 10% risk of maternal death is high.

Therefore, patients with cirrhosis should be monitored by a team including an obstetrician and a hepatologist, and should undergo endoscopic evaluation for varices because portal hypertensive events worsen during pregnancy, especially in the second trimester and peripartum. Propranolol is safe during pregnancy. If the patient's Model for End-Stage Liver Disease score is higher than 10, she is more likely to have variceal bleeding, ascites, or encephalopathy, as well as a higher mortality.

G&H Following delivery, is there typically a change in the mother's disease activity?

MP Flares are twice as common in the postpartum period as during pregnancy, and they occur in approximately

20% to 50% of patients following delivery, which is a fairly high rate. Therefore, the mother's liver tests and immunoglobulin G level should be measured at delivery and then 4 to 6 weeks later. Patients are usually monitored for a flare every 6 weeks during the first 3 months postpartum and then return to normal monitoring depending on the activity of AIH.

G&H Why is there an increase in the likelihood of flare following delivery?

MP It is thought that women are immunosuppressed during pregnancy and when they deliver, their immune system is augmented, which may lead to flares.

G&H Can AIH treatment also continue safely during breastfeeding?

MP Although breastfeeding is not recommended by the package insert of azathioprine, most medical societies recommend continuing azathioprine during breastfeeding because drug levels have been shown to be very low or undetectable in breast milk samples. Breastfeeding is also safe with prednisone. There are no data on budesonide and breastfeeding.

G&H Should women with AIH who are planning to become pregnant take any particular steps in preparation?

MP First, they should discuss with their obstetrician and their hepatologist that they want to become pregnant. The best time for hepatologists to counsel patients is early, prior to pregnancy. Second, patients should make sure that they have good control of their AIH prior to conceiving. AIH patients who are planning to become pregnant should know that the best pregnancy outcomes are associated with AIH disease that has been well controlled for at least 1 year. Third, these patients should be checked for thyroid disease. A number of AIH patients also have abnormal thyroid function, which can negatively impact pregnancy.

G&H What are the next steps in research?

MP It would be helpful to study larger cohorts of pregnant AIH women because much of the data (including the cirrhotic data) come from patients without AIH. In addition, the data on breastfeeding and monitoring come from very small studies. It would be most beneficial to have large national or international cohorts, such as those that have been conducted for primary biliary cholangitis, which would allow hepatologists to answer many of the questions that patients have.

Dr Peters has no relevant conflicts of interest to disclose.

Suggested Reading

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