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REVIEW

Autoimmune hepatitis and pregnancy

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INTRODUCTION

Autoimmune hepatitis (AIH) is an immune-mediated liver disease, characterized by an aberrant innate and adaptive immune response that targets autoantigens in both hepatocytes and biliary epithelium, causing a state of inflammation. It more frequently affects women, especially during their reproductive years, and can complicate pregnancy. During gestation, secondary to the unique immune mechanisms that allow for tolerance of the fetus, AIH remission can be achieved. This is thought to be secondary to the rise in estrogen and progesterone, which suppress the expression of T-helper (Th) 1-associated and Th17-associated cytokines, stimulate differentiation of Th0 to Th2 cells, and induce regulatory T cells. Such a shift from Th1/Th17 proinflammatory cells to a Th2/Tregs anti-inflammatory state promotes immune tolerance in pregnancy. However, once the tolerogenic immune state of pregnancy reverts following delivery, 13%–55% of patients will experience a flare (Figure 1).[1,2]

AIH can also present de novo during pregnancy and in the postpartum period; it usually has an insidious course with elevated transaminases, but severe acute hepatitis is seen in 25% and acute liver failure in 6% of cases.[3]

Fertility is frequently affected in patients with chronic liver disease, and poorly controlled AIH has been associated with lower fertility rates.[4] In patients with AIH, *in vitro* fertilization/embryo transfer has resulted in successful pregnancies. In one of the largest studies of *in vitro* fertilization in women with liver-related subfertility, 75% of *in vitro* fertilization cycles resulted in successful implantation, with a live birth rate of 74%.[5] Pregnancy can also be achieved after a liver transplant, as most patients will have restored fertility after transplantation.

Liver-related, obstetric, and perinatal outcomes

Pregnancy outcomes in women with AIH have improved over the past decade. Although early studies suggested high rates of maternal and fetal complications, a better understanding of preconception risk factors combined with cumulative safety data for medication use in pregnancy culminated in more favorable outcomes.

It is now well-known that patients with untreated AIH and those with shorter biochemical remission time (< 12 mo) at the time of conception are at an increased risk for flare-ups and hepatic decompensation during pregnancy.[4,6] Women with cirrhosis are at higher risk for death/liver transplantation during or within 12 months of delivery, and the loss of biochemical response during pregnancy increases this risk.[4] Regardless of the etiology of cirrhosis, 1.6% of pregnant women with compensated cirrhosis experience hepatic decompensation, especially variceal bleeding, which in turn is associated with increased rates of preterm birth, small-for-gestational age, and neonatal respiratory distress.

Gestational diabetes (4.7%–17%)[3,7,8] and hypertensive complications (7.3%–9%)[8,9] are more commonly reported in pregnant women with AIH in comparison to healthy women; the risk of gestational diabetes is only in part related to the use of corticosteroids for the treatment of AIH.

In addition to retrospective studies, several population-based and nationwide studies confirm an association between AIH and a higher risk of preterm birth, with reported rates between 6% and 20%.[8–10] The association with low birth weight and small-for-gestational age is less consistent. However, a recent meta-analysis

Abbreviations: AIH, Autoimmune hepatitis; CNI, calcineurin inhibitors; IVF, In vitro fertilization; MELD, Model for end-stage liver disease; MMF, mycophenolate mofetil; mTOR, Mammalian target of rapamycin; Th, T helper.

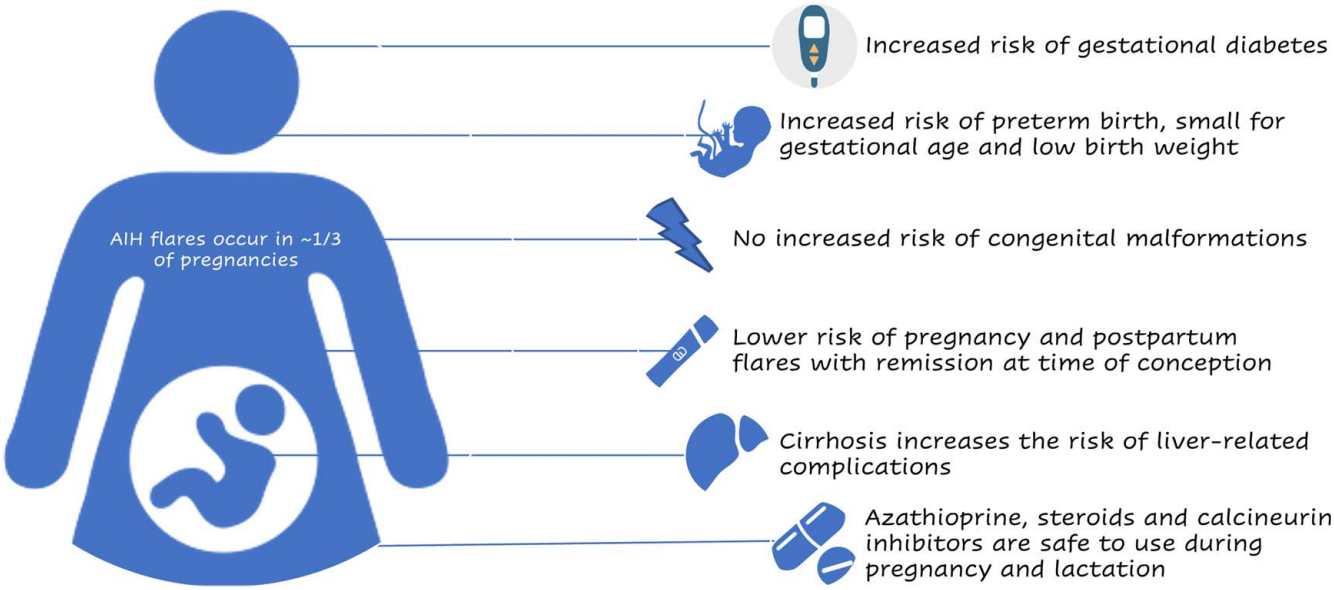

FIGURE 1 Important concepts regarding autoimmune hepatitis and pregnancy. Abbreviation: AIH, autoimmune hepatitis.

including data from 14 studies, with a total of 1452 patients with AIH and 1556 pregnancies, found an increased likelihood of small-for-gestational age births and low birth weight in addition to gestational diabetes and preterm births.[7] Importantly, the risk of stillbirth, congenital abnormalities, and neonatal mortality is not increased.[8–10]

Severe acute fulminant hepatic failure secondary to AIH during pregnancy has been reported, with adequate response to immunosuppressive therapy when instituted early, but possibly resulting in pregnancy loss.[11]

Management strategies in pregnancy and breastfeeding

Preconception counseling is important to achieve good pregnancy outcomes. First, maintaining biochemical remission for at least 12 months before conception is associated with lower rates of flare-ups during pregnancy and postpartum (Figure 2). Discussing the risks and benefits of continuing immunosuppression will ease the patient's concerns and improve compliance. Second, this is the time to assess the severity of liver disease. The risk of hepatic decompensation and death should be communicated to the patient. Screening for esophageal varices should be performed before conception, if possible. If needed, endoscopy can be performed in the second trimester of pregnancy. Women with cirrhosis who receive preconception counseling are more likely to follow through with endoscopic surveillance and have better liver health compared to those who do not.[12]

Current guidelines support the continued use of prednisone and/or azathioprine, as well as calcineurin inhibitors during pregnancy, as these drugs have not

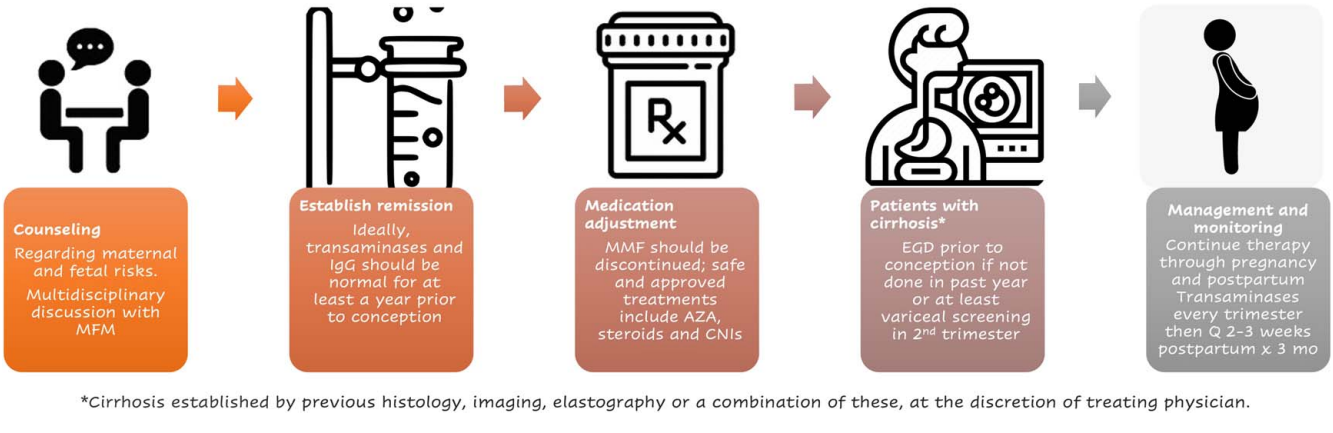

FIGURE 2 Preconception planning for patients with autoimmune hepatitis.*Cirrhosis established by previous histology, imaging, elastography, or a combination of these, at the discretion of treating physician. Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitor; EGD, esophagogastroduodenoscopy; MFM, maternal fetal medicine; MMF, mycophenolate mofetil.

been shown to cause an increased risk for premature births or congenital malformations.[2] Similarly, the use of prednisone and/or azathioprine while breastfeeding is safe; exposed children have age-appropriate mental and physical development, with similar infection rates for common childhood illnesses and no difference in rate of hospitalizations compared to those not exposed to azathioprine. Budesonide has also proven safe to use and well tolerated during pregnancy and breastfeeding.

Close monitoring is recommended particularly in the third trimester and postpartum period, when the risk of disease flare-up is the greatest (Figure 2). In case of loss of biochemical response during pregnancy, an increased dose of corticosteroids is recommended, and second-line or third-line options may be required.

While the use of glucocorticoids, tacrolimus, cyclosporine A, and azathioprine is considered safe in pregnancy, mycophenolate and mammalian target of rapamycin inhibitors must be discontinued. Mycophenolate use is associated with a high risk of congenital malformations and spontaneous abortions. In fact, it is recommended that women discontinue mycophenolate use at least 6 weeks before attempting conception.[2] Mammalian target of rapamycin inhibitors are not recommended due to the lack of sufficient human data.

In conclusion, while pregnancy and childbirth in AIH appear to be safe both for mother and child, even in cases of compensated liver cirrhosis, adequate prenatal care and monitoring are paramount to decrease the rate of complications. A summary of important concepts in AIH and pregnancy is presented in Figure 2.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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