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Pregnancy and autoimmune hepatitis

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Abstract

Autoimmune hepatitis is a rare condition that is more common among women than men. An association between pregnancy and autoimmune hepatitis is rare. This clinical scenario requires the gastroenterologist and hepatologist to have a profound knowledge of clinical course counseling and medical management. The prognosis in well-controlled and closely monitored patients is good. In this review, we discuss the most important aspects of autoimmune hepatitis and pregnancy as part of the Symposium on Liver and Pregnancy, co-sponsored by the Mexican Association of Hepatology and the Mexican Association of Gynecologists and Obstetrics.

Key words: Autoimmune hepatitis, pregnancy, fetal outcomes

Autoimmune hepatitis (AIH) is a rare condition that is more common among women than men. However, it occurs globally in children and adults of both sexes in diverse ethnic groups. This heterogeneity distinguishes AIH from other chronic liver diseases,[1] and makes it an important topic for gastroenterologists and hepatologists. Knowledge of the clinical course of the mother and the pregnancy is important, particularly considering the ethical issues involved in the therapeutic options. In this review, we discuss the most important aspects of AIH and pregnancy as part of the Symposium on Liver and Pregnancy, co-sponsored by the Mexican Association of Hepatology and the Mexican Association of Gynecologists and Obstetrics.

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The real setting

Childbirth can be the most dangerous moment in life for both mother and baby. For anyone who has been through the experience, or seen someone else go through it, there is no doubt that childbirth is a life-changing event. The suffering associated with childbirth contributes to a significant portion of the world's overall tally of ill-health and death. Most of the deaths and disabilities attributable to childbirth are avoidable, because the medical solutions are well known.

Maternal mortality is currently estimated at 529,000 deaths per year, a global rate of 400 maternal deaths per 100,000 live births. There are immense variations in these death rates in different parts of the world. Maternal deaths are even more inequitably spread than newborn or child deaths. A tiny 1% of maternal deaths occur in the developed world. Maternal mortality rates range from 830 per 100,000 births in African countries to 24 per 100,000 births in European countries. Of the 20 countries with the highest maternal mortality rates, 19 are in sub-Saharan Africa. Regional rates mask very large disparities between countries. Regions with low overall mortality rates, such as the European region, contain countries with high rates. Within one country, there can be striking differences between subgroups of the population. Rural populations suffer higher mortality rates than those of urban dwellers. Rates can vary widely with ethnicity and wealth, and remote areas bear a heavy burden of deaths.[2]

Despite this scenario, AIH is a rare cause of maternal morbidity. Until 2004, only 17 cases describing the association of AIH and pregnancy had been identified in reports and series,[3] probably indicating underdiagnosis of this entity.

Immunity and pregnancy

The success of human pregnancy, in which the fetus grows comfortably within the maternal uterus for nine months, defies the precepts of immunology. Pregnancy is a homeostatic state wherein genetically different fetal tissues attach to the mother without triggering acute rejection. A vast array of immunological mechanisms underlie this phenomenon *(Table I)*, and are as yet incompletely understood. Previously, the lack of a strong maternal cellular immune response or the more dominant humeral immune response toward the fetus was thought to account

for maternal acceptance of the fetal allograft.[4] However, during pregnancy, the maternal immune system is clearly active, and under certain conditions may contribute to fetal damage or death. Yet, even with a demonstrably active maternal immune system, mothers usually tolerate rather than reject their genetically disparate fetuses. Ordinarily, the mother would be expected to generate graft-attacking antibodies and cytotoxic T lymphocytes to foreign (paternal) human leukocyte antigen (HLA) or other antigens expressed by fetal cells. HLA antigens are called "transplantation" antigens because they are the most powerful stimulators of graft rejection. Thus, in organ transplantation, the matching of certain donor and patient alleles is an absolute requirement for successful grafting.[5]

Since the first report by Medawar in the 1950s, many possibilities have been suggested to explain why the semiallogeneic fetus is not rejected by the mother. The suggestion of Medawar that no fetal antigen is expressed that activates maternal cells appears to be true. However, this lack of stimulation of maternal cells by antigens is not due to an anatomical separation of the fetal and maternal cells, because maternal cells and fetal trophoblast cells are in close contact in both the decidua and the peripheral circulation. Instead, the trophoblast cells in contact with the maternal (immune) cells do not express major histocompatibility complex (MHC) Ia antigens and are therefore not recognized as "non-self" by maternal T lymphocytes. To escape lysis by uterine natural killer (NK) cells, the trophoblast cells express the MHC Ib antigens, HLA-E and HLA-G. Moreover, if immune cells do become activated in the presence of trophoblast cells, the trophoblast cells are able to induce apoptosis in these activated immune cells, because they express apoptosis-inducing ligands, such as FasL and TRAIL.[6]

Course of the AIH during pregnancy

In the study by Candia et al,[3] in which they analyzed 101 pregnancies, they found 47 flare-ups of AIH, 35 occurring during pregnancy and 12 following delivery. Five were associated with clinical improvement, 45 stabilized after treatment, and in four cases, the clinical course was not recorded. Recently, Schramm et al[7] published the experiences of 22 patients with AIH in Germany. They reported that maternal death or transplantation was observed in 9% of patients, flare during pregnancy in 21%, postpartum flare in 52%, and biochemical remission at conception in 73% of patients. Interesting observations were that 21% of flares presented at a median gestational age of 12 weeks, 52% of flares occurred at a median gestational age of three months after delivery, and there was no difference in the rate of flares in first and subsequent pregnancies. This and other reports[8–10] indicate that patients should be monitored closely in the postpartum period. An important observation made in this series was that women with cirrhosis or bridging fibrosis had a stable course, in contrast to other chronic liver diseases.[11] Unfortunately, in this and other series,[12–14] no factors predictive of flares were identified.

Table I. Modifications to the maternal immune system during pregnancy. Modified from Aagaard-Tillery et al.[20]

Component	Alteration
B cell numbers	no change
T cell numbers and subsets	no change
T cell function	decreased
NK cell function	decreased
IgG, IgM, IgA	no change
Antibody-dependent cellular cytotoxicity	no change
Complement	no change

Course of pregnancy in mothers with AIH

A review of the literature shows that fetal outcome in babies born to mothers with AIH is highly variable. In one review, a fetal death rate of 19% and a perinatal mortality of 4% were reported. Most fetal deaths occurred before the 20th week of pregnancy.[3] One of the most common adverse outcomes in women with AIH is preterm delivery (17% *vs* 6% in the general populations in developed countries). The rate of adverse pregnancy outcome was 26%[7] and the rate of fetal loss varied from 14.3%[12] to 24%.[7]

Although there are no reports of an elevated rate of congenital malformations in progeny born to women with AIH, pyloric stenosis,[15] fetal heart block,[16] Edward's syndrome, the Smith–Lemli–Opitz syndrome, spastic tetraparesis,[7] and Perthes' disease of the hip[12] have been reported.

According to the available information, AIH with compensated cirrhosis can be controlled during pregnancy in women who adhere well to an appropriate immunosuppressive regimen, with favorable perinatal outcomes.[17]

Medical management concerns

Despite the improved clinical course of AIH during pregnancy, most patients require pharmacological treatment for both stable disease and flares. Therefore, it is necessary identify those drugs that have some deleterious effect on the fetus *(Table II and Table III)*.

The use of purine analogues is probably the most important issue in the treatment of AIH during pregnancy. Population-based prescription studies in women with inflammatory bowel disease showed an odds ratio of having a child with congenital malformations while on azathioprine of 3.4.[18] This has not been demonstrated in patients with lupus receiving azathioprine.[19] However, recent information suggests that the continuation of low-dose treatment may be justified in well-controlled pregnant patients.[7] However, it must be kept in mind that the fetus is

Table II. Food and Drug Administration categories of drugs used during pregnancy

Category	Interpretation
A	Controlled studies show no risk
B	No evidence of risk in humans Animals findings show risk but human studies do not OR Animal studies are negative but there are no adequate human studies
C	Risk cannot be ruled out Animal studies are positive or lacking, human studies are lacking
D	Positive evidence of risk Can still be used if benefit outweighs risk
X	Contraindicated during pregnancy

Table III. AIH medications: summary of recent safety data.

Medication	FDA pregnancy category	Recent safety data during pregnancy
Corticosteroids		
Prednisone	*C*	Generally well tolerated and safe in pregnancy
Prednisolone	*C*	
Purine analogues		
Mercaptopurine	*D*	Seem safe for use during pregnancy
Azathioprine	*D*	
Immunosuppressives		
Cyclosporine	C	Seems safe for use during pregnancy. Associated with low birthweight and prematurity

exposed to a lower concentration of thiopurine metabolites, such as 6-thioguanine nucleotides, during pregnancy than is the mother. This reflects an important role of the placenta, which forms a (relative) barrier to azathioprine and its metabolites, insofar as 6-thioguanine nucleotides cross the placenta but 6-methylmercaptopurine does not. Some suggest that intrauterine exposure to high 6-thioguanine nucleotide levels may be avoided by therapeutic drug monitoring. However, in women who have previously used azathioprine with no reported adverse effects, it is probably safe.[12]

Finally, because flares occur quite often after delivery, it seems wise to augment immunosuppressive therapy soon after parturition. Breastfeeding during treatment with azathioprine is not recommended, although only 1.2% of the absorbed amount of azathioprine seems to be excreted in breast milk. However, in a recent report of six women with kidney transplants who were taking azathioprine during breastfeeding, no adverse effects were described in the newborns. Therefore, the drug was reclassified as "probably safe" for breastfeeding neonates.[8]

Conclusions

Pregnancy is associated with modifications of the mother's immune system. Despite these changes, the clinical course of AIH and the fetal outcomes are good. These patients should be closely monitored, particularly during the postpartum period. The goal of medical treatment is to achieve biochemical improvement with the lowest doses of drugs, and some caution should be exercised in the breastfeeding period.

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