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Case Report

Hydralazine-Induced Liver Injury in Pregnancy: A Case Report

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Abstract

Hydralazine is a commonly used oral antihypertensive agent. We report a rare case of hydralazine-induced hepatotoxicity in pregnancy. The patient, aged 28 years, G3P2A0, presented history of gestational diabetes mellitus at the 14th week of pregnancy, and received insulin and folic acid replacement under follow-up with the obstetrician. She was diagnosed with pregnancy-induced hypertension at 15 weeks gestation. She initially received 2 antihypertensive drugs, hydralazine and methyldopa. After that controlled blood pressure well, methyldopa was stopped, leaving only hydralazine as the antihypertensive drug.

The dosage of hydralazine was 75 mg daily, and the drug was initiated about 4 months before the abnormal symptoms began. Symptoms, signs, and laboratory results were compatible with hepatitis, hepatocellular form. She presented no history of using herbal medicines and did not show results from tests for viral hepatitis A, B, and C and autoimmune hepatitis. To establish hydralazine-induced liver injury diagnosis, we used the assessment tool outlined by the Council for International Organization of Medical Sciences (CIOMS) scale that led to a "probable" relationship.

One week after discontinuing hydralazine, the symptoms improved. The liver function test (alanine transaminase) decreased by approximately 50% within 1 week of discontinuation and was normal in the second week after stopping the drug. Finally, the antihypertensive drug could be stopped after the postpartum period.

Keywords: *Hydralazine; Pregnancy; Liver Injury; Hepatitis*

Introduction

The incidence of abnormal liver function tests (LFTs) among pregnant women is approximately 3 - 5%. However, the resulting liver function abnormalities should be appropriately assessed because there may be disorders of the disease pending diagnosis that may require additional treatment in the mother and infant, such as herpes hepatitis or viral hepatitis B [1].

In most cases, liver function among pregnant women was at normal range similar to those in non-pregnant women. Although placenta production increased, including alkaline phosphatase (ALP), alpha-fetoprotein or affected by plasma increase, albumin and hemoglobin values decreased. Studies need to investigate further to determine if the levels of aspartate transaminase (AST), alanine transaminase (ALT), or bilirubin increased [1,2].

In an initial evaluation of pregnancy with hepatic impairment, subjects should be divided in two groups as detailed below:

1. Pre-existing disease in pregnancy or those not directly related to pregnancy: including various types of hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis E, herpes simplex virus), cirrhosis, and other liver diseases such as autoimmune hepatitis (AIH), primary biliary cirrhosis, Wilson's disease, and drug/herbal causes [1].

2. Liver diseases unique to pregnancy: severe morning sickness (hyperemesis gravidarum), intrahepatic cholestasis of pregnancy, acute fatty liver disease of pregnancy, pregnancy induced-hypertension (preeclampsia, eclampsia), and HELLP syndrome [1].

In the first step of the assessment, approach to pregnant women with abnormal liver function (LFTs) is the same for nonpregnant women, including a detailed history, physical examination, and laboratory testing. However, depending on the type of hepatocellular hepatitis, differential diagnoses should also consider drug and herbal causes.

Case Details

The patient, aged 28 years, G3P2A0, presented history of gestational diabetes mellitus at the 14th week of pregnancy, receiving insulin and folic acid replacement, under follow-up with the obstetrician. The pregnancy-induced hypertension was diagnosed at the 15th week of pregnancy. She received hydralazine and methyldopa. After that controlled blood pressure well, methyldopa was stopped at the 23rd week of pregnancy, leaving only hydralazine as the antihypertensive drug.

She started prenatal care at the 12th week of pregnancy and satisfactory evolution was observed up to the 35th weeks when she reported to the prenatal care department with abdominal discomfort, nausea, vomiting, and fatigue (for one week) without fever or jaundice and pruritus throughout the body. She was started on hydralazine 50 mg 3 times daily for 18 weeks and discontinued methyldopa 12 weeks later. She had no history of liver disease, and liver function tests exhibited the usual results before initiating hydralazine.

Table 1 shows the patient clinical evolution during prenatal care based on gestational age. Table 2 offers the patient's laboratory and serology at admission, and table 3 presents LFTs before initiating hydralazine, at admission and 1 - 3 weeks after stopping hydralazine.

Laboratory	Quarter		
	First	Second	Third
Hemoglobin (g/dl)	13.2	10.5	11.7
Hematocrit (%)	35.9	31	34.6
Normal lymphocytes (%)	36.2	40.2	35.5
Platelets (x1000)	407	392	373
Peripheral blood smear	N*	N*	N*
Glucose	150	122	98
Creatinine (mg/dL)	0.4	0.32	0.44
Urine analysis	Normal	Normal	Normal
Urine protein 24 hours (mg/day)	132	118	144
Syphilis	Negative	Negative	Negative
HIV	Negative	Negative	Negative
Free thyroxin (ng/dL)	0.98	1.02	0.87
Hepatitis B immune	Immune	-	Immune

Table 1: *Prenatal exams.*

**N= No Hemolytic Blood Picture.*

Serology	Results
HBsAg	Negative
Anti-HBc	Negative
Anti-HCV	Negative
HAV (anti-HAV-IgM, anti-HAV-IgG)	Negative
EBV (anti-EBV-IgM, anti-EBV-IgG)	Negative
HEV (anti-HEV-IgM, anti-HEV-IgG)	Negative
HSV (anti-HSV-IgM, anti-HSV-IgG)	Negative
VZV (anti-VZV-IgM, anti-VZV-IgG)	Negative
Antinuclear antibody	Negative
Smooth Muscle Antibody (SMA)	Negative
Liver kidney microsomal type 1 (LKM-1) antibody	Negative

Table 2: *Patient's laboratory and serology.*

Event/LFT	Albumin (g/dL)	Globulin (g/dL)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)
Before treatment	4.0	3.3	0.7	0.2	36	28	70
At admission	4.0	3.8	0.7	0.4	238	478	136
Day 3 after discontinuation	3.1	3.3	0.6	0.3	114	320	101
Day 7 after discontinuation	2.9	3.1	0.2	0.2	56	179	95
Day 18 after discontinuation	3.3	3.3	0.4	0.2	32	22	105

Table 3: *LFTs before initiating hydralazine, at admission, and 1-3 weeks after stopping hydralazine.*

On examination, her vital signs on admission comprised temperature 36.5°C, pulse 106/minute, BP 160/95 mmHg, and respiration 18/minute. Generally, she appeared sick and dehydrated, with no evidence of distress/discomfort. Regarding HEENT, no scleral icterus was observed. Normal oral mucosa, and no lesions or chancres were observed. No cervical/supraclavicular lymphadenopathy and no thyroid enlargement was observed. Regarding CVS, normal S1/S2, and no murmurs, thrills, or heaves were observed. Regarding the respiratory system, the chest was clear with good air entry equal bilaterally, and no adventitious breath sounds. Concerning the abdomen, fundal height was 3/4 above the umbilicus, and fetal heart sounds were favorable at 144 beats/min. No guarding or rebound tenderness and no hepatosplenomegaly was observed. Regarding the extremities, no edema, ecchymosis, or petechiae were noted and other signs were non-remarkable.

Workup revealed elevated liver transaminases. Other etiologies including viruses, common toxins, drugs, autoimmunity and copper-induced hepatitis were excluded. Abdominal imaging studies did not show any evidence of intrahepatic or extrahepatic biliary ductal dilatation, and no pathologies were found in the liver and pancreas.

As we could not find any other cause of hepatitis, we attributed this to a side effect of hydralazine. Hydralazine was immediately discontinued. One week after discontinuing hydralazine, the symptoms improved. The liver function test decreased by approximately 50% within one week of discontinuation and was normal in the second week after discontinuation of hydralazine, as shown in figure 1. To

establish the diagnosis of hydralazine-induced liver injury, we used an assessment tool outlined by the Council for International Organization of Medical Sciences (CIOMS) scale that led to a "probable" relationship. Finally, the antihypertensive drug could be stopped after the postpartum period.

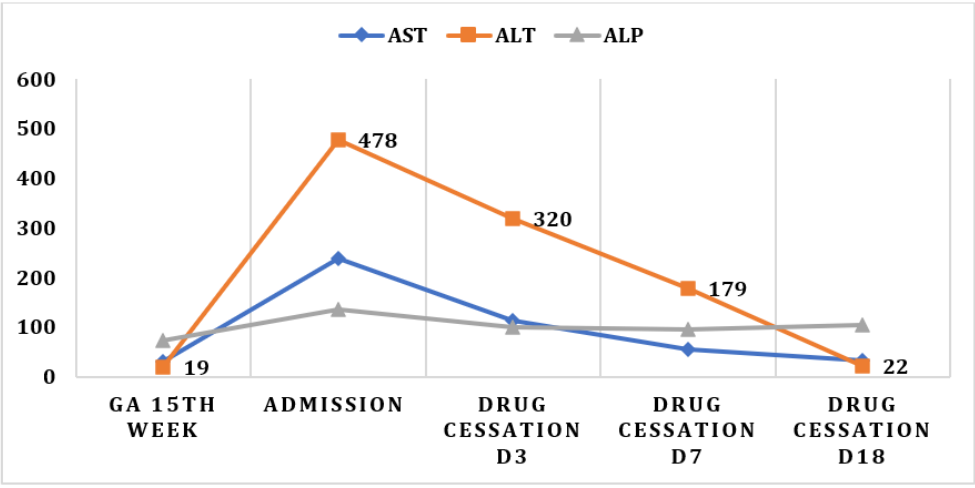

Figure 1: *Serum aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) levels before initiating hydralazine, during symptoms (at admission) and 1 - 3 weeks after discontinuing hydralazine.*

Discussion

The use of drugs among pregnant women is common in practice. During the gestation period, 59% of drugs were used, compared to 74.6% before pregnancy. Antibiotics were the most used drug, 26.1%, followed by antiemetics, 13.7%. However, the information from the European continent, North and South America, and Australia found that 35.8-56% of analgesics were used with 9.6 - 14% of antibiotics [3]. Most importantly, herbal use was found during pregnancy. The rate was very high in some countries such as Russia, Eastern Europe, and Australia, at 43.8 - 69% [4].

The international Council for International Organizations of Medical Sciences (CIOMS) expert panel defines liver injury as alanine aminotransferase (ALT) or alkaline phosphatase (ALP) levels at least twice normal (at least 2N) levels, where N is the maximum value of the normal) [5]. Consensus of the international Drug-induced Liver Injury (DILI) Expert Working Group in Europe, the US, and Japan define of liver injury at least five times the level of alanine aminotransferase (ALT) or increased at least three times with more than twice the standard value of bilirubin [6]. Medicines that cause liver toxicity, DILI, may induce liver failure [7].

The drugs that most caused DILI were antibiotics (45.4%), herbs and supplements (16.1%), and cardiovascular drugs (9.8%). Antibiotics that were associated the most with DILI was amoxicillin/clavulanate (10.1%), isoniazid (5.3%) and nitrofurantoin (4.7%). A higher DILI mortality was found in prior liver disease (16% and 5.2%, respectively) [7-9]. However, the list of drugs that are reported to be born idiosyncratic DILI mostly concern pregnancy. The information is shown in table 4.

Primary implicated agent	Percentage in series	Percentage in female
Herbal/dietary supplements	16.10%	-
Amoxicillin/clavulanic acid	10.10%	41%
Isoniazid	5.30%	67%
Nitrofurantoin	4.70%	100%
Sulfamethoxazole with trimethoprim	3.40%	45%
Cefazolin	2.20%	50%
Azithromycin	2.00%	72%
Phenytoin	1.30%	-
Methyldopa	1.20%	-
Hydralazine	1.00%	-
Amoxicillin	0.70%	-
Amiodarone	0.60%	-
Carbamazepine	0.40%	-
Metformin	0.30%	-
Propylthiouracil	0.30%	-
Ranitidine	0.30%	-
Vancomycin	0.30%	-
Verapamil	0.30%	-
Clindamycin	0.20%	-
Erythromycin	0.20%	-
Methylprednisolone	0.20%	-
Pyrazinamide	0.20%	-
Valacyclovir	0.20%	-

Table 4: *List of reported drugs in idiosyncratic DILI more common in pregnancy [7,29].*

The five main drug groups reported causing DILI among pregnant women are antihypertensive, antithyroid, antiretroviral, tuberculosis drugs, and antibiotics [7].

The antihypertensive drugs reported to be associated with DILI include only labetalol, methyldopa [10-13] and hydralazine [14-17]. Methyldopa has been more reported to induce hepatotoxicity in pregnancy [10-13] and may be used frequently in pregnancy and provide safety for the fetus.

Hepatitis has been reported among pregnant women using methyldopa both before and after pregnancy [10-13] or for the first time within the first 20 weeks of pregnancy to treat hypertension [18-20]. The dose administered did not exceed the maximum recommended dose (500 - 1,500 mg per day). Symptoms appeared between 2 and 12 weeks later [13] and the diagnosis was isolated from infectious and autoimmune hepatitis [13,21]. Although recovery occurs spontaneously after a short stoppage of the drug, it may require steroid use in some cases.

The hepatotoxicity in this patient exhibited a hepatocellular pattern and based on Hy's prognosis was predicted to have a 10% mortality rate [8]. This patient presented no history of liver disease and normal liver function before initiating hydrazine. In addition, other causes of hepatitis were not found, such as infection, herb intake, autoimmunity, and hepatitis caused by copper. No evidence indicated abdominal or extracranial bile duct enlargement and no pathology was observed in the liver and pancreas from ultrasound. Eventually, the patient recovered after two weeks of discontinuation, supporting the diagnosis of drug-induced hepatitis.

The results of the RUCAM causality assessment method [22] and Council for International Organizations of Medical Sciences scale (CIOMS scale) [23] were 8 points and 7 points, respectively. Drug-induced hepatitis from hydralazine was believed (probable) [22,23].

Hydralazine was first used in the 1950s as it provided peripheral vasodilation and antihypertensive effects. Generally starting at 10 mg four times daily, the maximum dose was 200 mg daily. The most common side effects included dizziness, headache, epigastrium pain, and nausea [24,25]. The hepatotoxicity of hydralazine has been rarely reported.

In prospective studies from 1988 to 2007 among 1,198 patients, 133 drug-induced hepatotoxicities were observed, but only one was caused by hydrazine [14]. One 12-year study among 313 patients found no reports of hepatotoxicity from hydralazine [26].

Hydralazine hepatotoxicity produces two clinical syndromes: a short latency period (2 - 6 weeks after drug use) and a long latency period (after using the drug for more than two months until one year) [15]. Clinical signs often include hepatocellular forms [24], but cholestatic patterns have also been reported [16,17]. In short-latency patterns, patients often experience rapid and severe symptoms, such as fever, rash, and eosinophilia, which also improve rapidly after stopping the drug. In the long latency period pattern, the symptoms were gradual, chronic hepatitis and fibrosis and autoantibodies were often detected in hydralazine-induced cholestatic. After stopping the drug, symptoms and liver function return to normal [16,27].

Hydralazine is an antihypertensive drug that is frequently used in practice, especially in pregnancy. However, it causes very rare hepatotoxicity and is associated with pregnancy. Occurrence is characteristic of idiosyncratic DILI found in only 1% and distinct dose-independent in nature. Many reports used the usual dose [16] and showed no predictive factors of hepatotoxicity, which can produce results from 1 day to 1 year after initiating the drug [27]. The differential diagnoses are hepatitis and autoimmune hepatitis [7-9,28].

Our patient was diagnosed with pregnancy-induced hypertension at 15 weeks gestation. She initially received two antihypertensive drugs, hydralazine and methyldopa. After that controlled blood pressure well, methyldopa was stopped, leaving only hydralazine as the antihypertensive drug.

The dosage of hydralazine was 75 mg daily, and the drug was initiated about four months before abnormal symptoms began. Symptoms, signs, and laboratory results were compatible with hepatitis, hepatocellular form. She presented no history of using herbal medicines and did not show further test results for viral hepatitis A, B, and C and autoimmune hepatitis. Our diagnosis suggested hydralazine-induced-hepatitis. In this case, the clinical signs included a long latency period experiencing symptoms after more than two months with insidious indicators. The prognosis was moderate because ALT was five times greater and indicated clinical hepatitis [6]. One week after discontinuing hydralazine, symptoms improved. ALT decreased by approximately 50% within one week of discontinuation and was normal in the second week after stopping the drug. Following up the patient until delivery, the fetus was small for gestational age (SGA) due to slow fetal growth (intrauterine growth restriction) from maternal high blood pressure. Finally, the antihypertensive drug could be stopped after the postpartum period.

Conclusion

Hydralazine is an antihypertensive drug commonly used among pregnant women. The common side effects include dizziness, headache, epigastrium pain, and nausea. The results causing hepatitis are scarce and does not depend on the dose used. Additional side effects may be found after two to six weeks or after using the drug for more than two months to one year. However, both can occur in hepatocel-

lular and cholestatic forms. Evaluation should be examined for other common causes, including viral hepatitis, autoimmune hepatitis, and herbal medications. In the case of investigating a suspected drug, stopping the medicine and monitoring signs and symptoms and LFT testing is recommended. LFT testing returns to normal within two weeks of stopping the drug, and symptoms improve in one week.

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Conflict of Interest

The authors declare they have no conflict of interest.

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