LETTER TO THE EDITOR

JOURNAL OF Obstetrics and Gynecological INVESTIGATIONS

J Obstet Gynecol Investig 2021; 4: e1–e4
DOI: https://doi.org/10.5114/jogi.2021.106111

Submitted: 10 February 2021
Accepted: 14 April 2021

Drug-induced liver injury in early pregnancy associated with methyldopa administration during antihypertensive therapy

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α-Methyldopa is one of the most common antihypertensive drugs used during pregnancy [1]. It is considered to be safe for the neonate and well tolerated by the woman [1, 2]. We present a case of drug-induced liver injury in a woman at 11 weeks' gestation who developed this rare complication as a result of methyldopa therapy. The diagnosis was made at an early stage, and thus, it made it possible to avoid more serious complications such as hepatic failure, liver cirrhosis or death. Noteworthy, the patient was treated with α-methyldopa during previous pregnancies, yet no side effects were observed. Due to the increasing incidence of gestational hypertension, there is a growing need to increase alertness of rare complications during antihypertensive therapy.

We analysed the medical history of the patient and searched MEDLINE database. Selection criteria included published data in English – case reports, original research and reviews. Articles related to hypertension in pregnancy or hepatotoxicity of α-methyldopa were selected and analysed.

A 41-year-old multipara was admitted to the Department of Perinatology in the 1st Chair of Obstetrics and Gynecology, Medical University of Lodz at 11 weeks' gestation due to elevated blood pressure (about 130/100 mm Hg). Such values of blood pressure maintained although she has been treated for hypertension with α-methyldopa (in a dose of 250 mg 3 times a day) for a month. Obstetric history included two pregnancies complicated by hypertension, resulting in delivery at term of two healthy neonates by cesarean sections. In routine examinations, 3 weeks prior to admission, all laboratory results were within normal limits (Table I). Laboratory tests at admission revealed elevated liver enzymes: alanine aminotransferase (ALT) increased to 325 U/l and aspartate aminotransferase (AST) to 290 U/l, while total bilirubin did not exceed the reference range – 0.3 mg/dl. Serum levels of bile acids were elevated to 15.8 mmol/l (upper limit of normal: 10 mmol/l). There were no abnormalities in the blood count and other biochemical tests such as electrolytes, amylase and prothrombin index. Slightly reduced serum levels of urea and total protein were observed. During the hospitalization, there was an upward trend in the biochemical parameters of liver injury (Table I). The symptoms

Table I. Liver function test in different gestational ages before the diagnosis

Parameter	Gestational age (GA)			
	8 GA[I]	11 GA[II]	11 GA	11 GA
ALT [U/l]	16	325.1	436.2	481.0
AST [U/l]	18	290.0	407.4	444.0
Bilirubin [mg/dl]	0.19	0.3	0.4	–
GGTP [U/l]	–	–	77.2	86
ALP [U/l]	–	–	89	90

[I]Without taking the medicine. [II]During α-methyldopa administration.

To cite this article: Opinc MD, Kalinka J. Drug-induced liver injury in early pregnancy associated with methyldopa administration during antihypertensive therapy. J Obstet Gynecol Investig 2021; 4: e1–e4. DOI: https://doi.org/10.5114/jogi.2021.106111

were mild and included headache, general malaise, nausea and abdominal distension. Routine measurements of body temperature were within normal limits, urine and stools were normal. No jaundice or pruritus was observed. The patient denied using alcohol, psychoactive drugs and other hepatotoxic medicaments and had no past medical history of liver disease. Medications in the current pregnancy included acetylsalicylic acid (150 mg), α-methyldopa (250 mg 3 times a day), and occasionally paracetamol. Due to the increased heart rate, the patient was consulted by a specialist of internal medicine and verapamil in a dose of 40 mg three times a day was added to the antihypertensive treatment. Abdominal ultrasonography revealed an enlarged, hyperechogenic liver with a cyst of 13 mm at the border of the lobes. In the uterine cavity, a single, alive fetus was developing properly. Due to the suspicion of autoimmune hepatitis, the patient was sent to the Infectious Diseases Hospital and underwent a series of laboratory tests, which excluded hepatitis A, B, C, E, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease. Drug-induced liver injury after α-methyldopa administration has been suspected. In our Department we often diagnose hypertension in pregnant women and implement treatment, usually with α-methyldopa, but so far we have not observed such toxic reactions. An interesting fact is that in both previous pregnancies the patient used α-methyldopa and no adverse effects were observed. During hospitalization the hypotensive treatment has been modified – verapamil was discontinued and the dose of α-methyldopa was gradually reduced. Blood pressure normalization has been achieved by the addition of a β-blocker (metoprolol) in a dose of 25 mg 2 times a day. After a shift in pharmacotherapy, a significant reduction in aminotransferases was obtained (Table II). Due to the improvement of the general health and normalization of laboratory parameters, there was no need to perform liver biopsy.

Results of control laboratory tests for 20 weeks' pregnancy remained within the normal range (Table II). Pregnancy was progressing properly. In the routine oral glucose tolerance test at 24 weeks of pregnancy, gestational diabetes was diagnosed (fasting glucose 99 mg/dl, after 1 h: 175 mg/dl and after 2 h: 176 mg/dl). Insulin therapy was administered.

At 34 weeks of pregnancy, the patient was referred to our department due to vomiting and cough. A 24-hour Holter blood pressure monitoring was performed, in which abnormal blood pressure values, especially diastolic blood pressure, were periodically observed. After another consultation by the specialist of internal medicine, verapamil was recommended once again (120 mg twice a day). Laboratory tests were within normal limits (Table II). After leaving the hospital, an ambulatory cardiological consultation was performed and an additional hypotensive medication, labetalol in a dose of 100 mg twice a day, was introduced to the therapy.

At 36 weeks of gestation, due to elevated blood pressure values up to 150/100 mm Hg, she was rehospitalized. As the diastolic blood pressure was constantly elevated, labetalol was increased to 100 mg 3 times per day. A course of antenatal corticosteroids was administered. Assessment of fetal circulation was performed with Doppler ultrasonography and revealed no abnormalities. Control tests of hepatic parameters were within normal limits (Table II). At 37 weeks of gestation because of sustained high blood pressure (above 140/100 mm Hg) the patient delivered by Caesarean section a female neonate. Neonate's birth weight was 2920 g and the umbilical arterial pH was 7.44.

In the postpartum period, the blood pressure values were periodically increased. The patient was discharged home with recommendations to maintain current antihypertensive therapy and refer to the outpatient clinic for control and possible modification of treatment. Control tests of liver parameters after childbirth remained within normal limits: alanine aminotranspherase (ALT) 8.4 U/l, aspartate aminotranspherase (AST) 19.2 U/l, bilirubin 0.2 mg/dl, γ-glutamyltransferase (GGTP) 12.2 U/l. However, biochemical parameters monitoring is necessary because cases of distant complications such as fibrosis leading to liver cirrhosis were described [3].

Liver diseases in pregnancy are not common and can be classified as pre-existing ailments, diseases unique to pregnancy and coincidental to pregnancy [3]. Pregnancy-related liver diseases are the most frequent causes of liver dysfunction in pregnancy [4]. Nearly 3% of pregnancies are complicated by liver disease [4]. A wide variety of liver pathologies makes these diseases difficult to differentiate. It is extremely vital to make the exact diagnosis and introduce appropriate treatment to reduce the mortality of pregnant women and neonates [4]. Taking drugs can be a frequently overlooked

Table II. Liver function test in different gestational ages after the reduction in the dose of α-methyldopa and discontinuation of verapamil

Parameter	Gestational age (GA)							
	11 GA		12/13 GA[III]	16/17 GA	19/20 GA	34 GA	34/35 GA	36/37 GA
ALT [U/l]	465.0	368.0	153.0	52	28.0	8	5.9	7.8
AST [U/l]	449.0	266.0	106.0	49	31.0	9	10.8	14.1
Bilirubin [mg/dl]	0.44	0.3	0.4	0.3	0.3	0.3	–	0.2
GGTP [U/l]	91	110	103	46	27	–	–	–
ALP [U/l]	92	–	86	72	67	–	–	–

[III]Discontinuation of α-methyldopa.

cause of liver pathology [3]. Drug-induced liver injury remains one of the most common causes of acute liver failure in the Western world [5]. There are over 1000 substances including medications, supplements and herbs that can cause liver damage [6]. Elevated values of liver function tests may result from dose-dependent hepatotoxicity, which is predictable and relatively frequent. On the contrary, idiosyncratic drug reaction is unpredictable and occurs less often (1 : 1000 to 1 : 100 000 cases) [7]. Several clinical manifestations of drug-induced liver damage were distinguished: transient asymptomatic elevation of transaminases, acute hepatocellular injury, acute cholestatic liver injury, mixed form and chronic liver damage [6].

The maternal alkaline phosphatase (ALP) and the α-fetoprotein (AFP) increase in pregnancy. Elevations in transaminases, bilirubin or the prothrombin time are abnormal and indicate a pathological state which requires further assessment [4].

About 5–10% of pregnancies globally are complicated by hypertension [8]. It is considered to be the second cause of death in pregnant women [8].

α-Methyldopa is considered to be a safe and well-tolerated drug without any influence on fetal hemodynamics and placental circulation [2, 7]. The initial dose is 250 mg 2–3 times a day during the first two days. It can be modified depending on the reduction of blood pressure. The maintenance dose is usually between 500 mg to 2 g/day, given 2–4 times a day. The maximum daily dose is 3 g [8]. Despite the fact that methyldopa is safe, side effects can affect all organs of the human body. Recent reports suggest also mental disorders such as postpartum depression in women using α-methyldopa [9]. The first case of liver injury during α-methyldopa therapy was described in 1969 (Elkington *et al.*) [10]. Data from the literature estimate the risk of developing hepatotoxicity while using α-methyldopa in pregnancy as about 1% [3]. The risk of developing such disorders in non-pregnant women ranges from 2.5% to 10%, being significantly higher in females as compared to males [3, 11].

Several cases of hepatopathy in pregnant women using α-methyldopa has been described so far. The mechanism of liver damage is caused by the abnormal metabolism of α-methyldopa by cytochrome P450. Through immunological processes the metabolite acting like an antigen induces an immune response [3, 6]. Liver defect may be temporary [11]. The drug can cause both acute and chronic liver failure [12]. Fatal necrosis is extremely rare [13]. The severity of liver damage does not depend on the dose and duration of the therapy [3, 4]. Symptoms of liver pathology in pregnant women most often appear within the first 3 months of using the drug [3, 11]. Typically, patients present with prodromal symptoms like fever, nausea, vomiting, general malaise and loss of appetite [10, 12]. Late-onset symptoms such as jaundice, dark urine and pale stools may also appear [11]. Additional symptoms that may occur in patients include pruritus, rash, lymphadenopathy, arthralgia and myalgia [1]. However, hepatic disorder can have a subclinical course with only isolated elevation of biochemical markers of liver injury, as in the described case [2]. On the contrary, hepatic dysfunction may lead to life-threatening conditions [11].

Diagnosis is most often made by excluding other possible causes of liver damage: infectious, toxicological causes as well as other liver, gastrointestinal or autoimmune diseases [6]. For pregnant women, it is also important to exclude pregnancy-associated liver diseases such as pre-eclampsia and gestational cholestasis. It is necessary to perform imaging examination of the abdominal cavity. Abdominal ultrasound examination is usually the first-line examination, yet it rarely reveals any abnormalities [2, 11]. Sometimes it is necessary to extend the diagnostics to more specific imaging diagnostics such as computed tomography scan or magnetic resonance imaging [6]. In blood tests, besides the biochemical markers of liver damage, it is also important to monitor the parameters of the coagulation system [1, 4]. In some patients, in addition to elevated transaminases or cholestasis parameters we can observe eosinophilia, prolonged prothrombin time and increased level of immunoglobulins [1, 2]. A liver biopsy performed in some patients showed focal necrosis, infiltration of inflammatory cells, proliferation of the bile ducts, microscopic features of cholestasis or liver cirrhosis, but in several cases no changes were found in histopathological examination [12]. Biopsy is not indispensable for the diagnosis.

α-Methyldopa hepatic injury usually subsides spontaneously after discontinuation of treatment. However, in some cases glucocorticosteroid therapy is recommended [6]. In the described case, biochemical parameters returned to norm quickly and steroid therapy was not necessary. Due to the increasing incidence of hypertension in pregnancy and the widespread use of antihypertensive therapy with α-methyldopa, it is important to diagnose early drug-induced complications. Due to the fact that this is a rare and unpredictable side effect, it is reasonable to perform liver function tests before and during treatment with α-methyldopa. As the case of hepatotoxicity in the woman 8 weeks after the delivery was reported, monitoring of patients during the postpartum period should be also considered [2]. Re-administration of the medicine after recovery may lead to fatal consequences [11]. Although in the majority of cases, α-methyldopa hepatic injury subsides without permanent consequences, cases of cirrhosis, liver transplantation, as well as the development of both benign and malignant liver tumors were also described [14].

In conclusion, hypertension is the most frequent medical problem in pregnancy with an upward tendency. Although α-methyldopa is considered as a safe therapeutic option, caution is needed when initiating therapy. It is advisable to monitor treatment for the safety of pregnant women, even if antihypertensive therapy with α-methyldopa was used without complications in previous pregnancies. α-Methyldopa-induced liver injury is a rare complication in pregnancy, but it can be associated with a serious prognosis.

Conflict of interest

The authors declare no conflict of interest.

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