

Pawłowska, Paulina, Ozga-Stachurska, Alicja, Wójcik-Grudzień, Justyna, Rozenbajgier, Martyna. The use of metformin in the treatment of Intrahepatic cholestasis of pregnancy. *Journal of Education, Health and Sport*. 2022;12(9):428-432. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2022.12.09.048> <https://apcz.umk.pl/JEHS/article/view/39712> <https://zenodo.org/record/7047506>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences). Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przynależność dyscypliny naukowej: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.08.2022. Revised: 20.08.2022. Accepted: 04.09.2022.

The use of metformin in the treatment of Intrahepatic cholestasis of pregnancy

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Abstract

Introduction: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disease. It is characterized by persistent pruritus, usually occurring after 30 weeks of

pregnancy, and by elevated levels of bile acids and transaminases, which decrease over the course of 2-3 weeks postpartum. [1,2]The occurrence of ICP in the mother may be associated with significant complications in the fetus, such as: preterm labor, intrauterine asphyxia, or sudden fetal death. Currently, the treatment of choice is ursodeoxycholic acid (UDCA).[2,6] Recently, it was observed that the administration of metformin in cases not responding to standard therapy improved lipid disorders in pregnant women.

The aim of the study: The aim of the study is to present the possibility of using metformin in the treatment of ICP in pregnant women not responding to standard treatment and to present a clinical case..

Material and methods: The work is a review of the literature on the management of ICP and the use of metformin in the treatment of lipid metabolism disorders, as well as a brief case report of a patient with intrahepatic cholestasis of pregnancy.

Description of the state of knowledge: Metformin is an oral antidiabetic drug belonging to the group of biguanides. However, the latest observations show that metformin also has a beneficial effect on the liver function and on the lipid metabolism in pregnant women. In these patients, the levels of bile acids and liver enzymes decreased after the use of metformin.

Summary: The mechanism of action of metformin explaining its beneficial effect on the lipid metabolism in pregnant women with intrahepatic cholestasis is not fully understood.

Key words: metformin, Intrahepatic cholestasis of pregnancy, lipid disorders, ICP

INTRODUCTION

Intrahepatic cholestasis of pregnancy is the most common reversible liver dysfunction in pregnancy. Its frequency in the Polish population is estimated at 1% - 2% of all pregnancies. It is common in South America (Chile - 6.5% to 22% of pregnant women), in Scandinavian countries, in Asian women. Cholestasis is likely to be undiagnosed many times; it is assumed that some unexplained fetal deaths are caused by ICP [1,2].

The first symptoms of cholestasis appear around 28-32 weeks of pregnancy. Symptoms persist up to 7 days after delivery (after 24-48 hours itching subsides, but in individual cases it persists for up to 2 weeks, then the biochemical indicators - ALT, AST, bile acid levels normalize). The risk of cholestasis recurrence in the next pregnancy is high, 40-100%. Symptoms - usually more intense in the next pregnancy, appear already around 22 weeks. Older women, multiple pregnancies, family

predisposition as well as hepatitis C and cholelithiasis in the past belong to the group at higher risk of developing severe intrahepatic cholestasis. [1,2,3,6]

SYMPTOMS

The main and often only symptom is pruritus without a skin rash, it usually begins in the second or third trimester (after week 30), worsens usually at night, is diffuse and often affects the palms and the soles of the feet. Due to its duration (night hours), it can lead to insomnia and irritability [2,3]

Additionally, there may be abdominal pain, nausea and vomiting, jaundice rarely occurs, fatty stools with impaired fat absorption (vitamin K deficiency), prolonged prothrombin time with perinatal bleeding [1,2,6]

Abnormalities in the results of laboratory tests concern the level of liver enzymes - aminotransferases: aspartate, alanine and γ -glutamyltranspeptidase (AspAt, AlAt and GGTP) and elevated levels of bile acids. Due to the level of bile acids in the blood, intrahepatic cholestasis in pregnant women can be divided into:

- 10 $\mu\text{mol} / \text{l}$ to 39 $\mu\text{mol} / \text{l}$ mild
- 40 $\mu\text{mol} / \text{l}$ to 99 $\mu\text{mol} / \text{l}$ moderate
- over 100 $\mu\text{mol} / \text{l}$ heavy

Every pregnant woman diagnosed with this disorder must be closely monitored, and the results of laboratory tests, the clinical condition of the patient and the assessment of the well-being of the fetus determine our further management [1,6]

TREATMENT AND COMPLICATIONS

The drug of choice is ursodeoxycholic acid (UDCA), which is well tolerated by pregnant women, with no negative effects on mothers and fetuses / newborns.

Complications that may be caused by cholestasis include:

- preterm labor (19-60%),
- intrauterine hypoxia of the fetus,
- intrauterine death,
- meconium excretion into the amniotic fluid (27%),
- damage to the function of the fetal heart-conducting cells,
- fetal bradycardia,
- perinatal haemorrhage,
- flow reduction umbilical cord

respiratory distress syndrome (RDS),
 pneumonia,
 edema,
 intrauterine asphyxia (up to 44%)
 intrauterine death (04, -4.1%)

Deteriorating laboratory test results may be the basis for earlier induction of labor after the fetal lung has matured. The risk of immaturity in preterm delivery should be weighed against the risk of intrauterine fetal death. In contrast, in the case of mild, uncomplicated cholestasis, labor is induced at 37-38 weeks of gestation.

All symptoms resolve spontaneously within 2-3 weeks postpartum [1,2,3,6]

METFORMIN

Metformin is a hypoglycaemic drug that forms the basis of treatment for type 2 diabetes.

It affects the carbohydrate metabolism, but also lipid disorders, endothelial function, inflammation, oxidative stress and the hemostatic system. It reduces the production of glucose in the liver, increases the uptake of glucose by tissues and reduces its absorption in the intestines [4,5].

CASE REPORT:

On March 20, 2018, a 27-year-old patient with a diagnosis of intrahepatic cholestasis of pregnancy was admitted to the Independent Public Clinical Hospital No. 4 in Lublin. First pregnancy, 29 weeks pregnant. Symptoms: itching in both arms, vomiting and nausea. The symptoms did not improve despite the administration of ursodeoxycholic acid (UDCA). Liver parameters gradually increased. At 31 weeks of pregnancy, the doctors gave the patient 1.5 g of metformin (divided into three doses). Changes in hepatic parameters (ALT, AST) and bile acid levels before and after metformin administration are presented below.

week pregnancy	ALT (U/L)	AST (U/L)	Bile acids (μmol/l)
29 +5	290	136	45,5
30 +4	441	143	24,7
31+5	Metformin		
33+0	155	43	7,3
33+6	75	38	3,3

34:5	86	35	3,8
35+4	89	40	3,8
36+4	94	40	6,2

After administration of metformin, the parameters decreased (ALT, AST and bile acids). The patient's condition gradually improved. By 33 weeks of pregnancy, the itching had completely resolved. At 37 weeks of pregnancy, the patient gave birth to a healthy baby.

Summary

Metformin helps in the treatment of Intrahepatic cholestasis of pregnancy. However, the mechanism of action of metformin explaining its beneficial effect on the lipid metabolism in pregnant women with intrahepatic cholestasis has not been fully understood. This drug has not been approved for the treatment of gestational cholestasis. Ursodeoxycholic acid (UDCA) remains the first-line drug, which is safe for both the mother and the fetus [6]

Reference:

1. Milkiewicz P., Elias E., Williamson C., Weaver J. Obstetric cholestasis. *BMJ* 2002; 324: 123–124.
2. Lammert F., Marschall H.U., Glantz A., Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J. Hepatol.* 2000; 33: 1012–1021.
3. Lee R.H., Goodwin T.M., Greenspoon J., Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. *J. Perinatol.* 2006; 26: 527–532.
4. Grzybowska, M., Bober, J., & Olszewska, M. (2011). Metformin-mechanisms of action and use for the treatment of type 2 diabetes mellitus. *Postepy higieny i medycyny doświadczalnej (Online)*, 65, 277-285.
5. Julia Bijok, Małgorzata Bińkowska, Grzegorz Jakiel. Metformina w ciąży. *Polskie Towarzystwo Ginekologiczne. Ginekol Pol.* 2014, 85, 527-531.
6. Rekomendacje Zespołu Ekspertów Polskiego Towarzystwa Ginekologicznego dotyczące postępowania w wewnątrzwątrobowej cholestazie ciężarnych, prof.dr hab.Bożena Leszczyńska-Gorzelał, prof. dr hab.Jan Oleszczuk, dr Beata Marciniak, prof. dr hab.Ryszard Poręba, prof. dr hab.Przemysław Oszukowski, prof. dr hab.Mirosław Wielgoś, prof. dr hab.Krzysztof Czajkowski. *Ginekol Pol.* 2012, 83, 713-717.