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Original research article

MATERNAL AND FETAL OUTCOMES IN WOMEN RECEIVING URSODEOXYCHOLEIC ACID (UDCA) AS TREATMENT FOR INTRAHEPATIC CHOLESTASIS OF PREGNANCY (IHCP), A SINGLE CENTER EXPERIENCE: ARE WE DOING ENOUGH?

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Abstract: *Intrahepatic cholestasis of pregnancy (IHCP) is a common type of hormonally driven cholestasis in the late second or early third trimester of pregnancy. It's a reversible condition and has a genetic predisposition. This study aimed to analyze the maternal and fetal outcomes of women being treated with Ursodeoxycholic acid (UDCA) for IHCP. Seventy-five pregnant women with IHCP were included in this observational cross-sectional study, with a study duration of one year. SPSS software version 24.0 was used to analyze the data collected by the investigating officer. Laboratory and clinical parameters were assessed at presentation and after treatment. Results showed that 92% of pregnant women with IHCP had significantly raised serum bile acid levels. However, UDCA treatment caused complete resolution of itching in 57.7% of patients, reduced to mild in 40.4%, and moderate itching in 1.9% of patients. Mean Alkaline Phosphatase and ALT levels significantly decreased after UDCA treatment, with p-values of 0.001 and 0.004, respectively. The dose of UDCA required ranged from 10-25 mg/kg/day. A positive family history of IHCP was found in 36.5% of patients, while 33% had a history of IHCP in previous pregnancies, and 16% had twin pregnancies. The incidence of early delivery was high at 98%, with a mean gestational age of 36.4 weeks. Among these early deliveries, 8% had vaginal delivery, and 92% had C-sections. The indications of delivery were intractable itching and no improvement in LFTS in 15%, PROM and fetal distress in 21%, failed induction in 31%, previous cesarean in 23%, and other reasons in 10%. The study found that 99% of babies had good APGAR scores and no morbidity. However, 1% mortality was reported due to severe IHCP in the mother. In conclusion, UDCA treatment significantly improved physical and laboratory parameters and effectively treated IHCP. Early delivery had better maternal and fetal outcomes.*

Keywords: Intrahepatic, Cholestasis, Pregnancy

Introduction

IHCP is the most common, reversible type of hormonally driven cholestasis in the late second or early third trimester of pregnancy. One of the reversible forms of hormonally driven cholestasis is intrahepatic cholestasis of pregnancy (IHCP). It has a genetic predisposition, typically in the late stages of pregnancy (Himeles and Pomeranz, 2022; Natarajan et al., 2022; NIRMALADEVI, 2019). it is characterized by generalized itching, manifesting in palms and soles. It is diagnosed based on personal history and physical examination and confirmed by laboratory findings, i.e., Bile Acid and liver function tests (Shao et al., 2021).

One of the reversible forms of hormonally driven cholestasis is intrahepatic cholestasis of pregnancy (ICP). It has a genetic predisposition, typically in the late stages of pregnancy(Himeles and Pomeranz, 2022). It is the most prevalent liver disease associated with pregnancy (Natarajan et al., 2022; NIRMALADEVI, 2019). It manifests as generalized itching, starting from palms and soles in the late second and third trimester of pregnancy. However, there are no other cutaneous manifestations.

IHCP has a low occurrence in the Western world. There is no specific cause of IHCP; however, multiple factors have contributed to it. These include genetic, hormonal, and environmental factors. Intrahepatic cholestasis of pregnancy is diagnosed after excluding all other causes of cholestatic diseases based on physical and clinical examination and confirmed by laboratory investigations. Since IHCP is associated with increased fetal morbidity and complications, treatment should be initiated as early as possible. However, there are no long-term maternal complications related to IHCP due to poor fetal outcomes; timely diagnosis and management with ursodeoxycholic acid and early delivery of patients with IHCP are recommended.

A deficiency in the excretion of bile salts occurs in those affected, which raises the level of bile acids in the blood. Their deposition under the skin causes severe debilitating itching. [1] There is no specific etiology for this cholestatic disease [4]. Furthermore, ICP has an increased recurrence rate, implying that certain persons are genetically predisposed to intrahepatic cholestasis of pregnancy.

According to research, adenosine triphosphate binding cassette, subfamily B, member 4 (*ABCB4/abcb4*) gene, also known as multidrug-resistant protein 3 (MDR3), has been linked to IHCP in 15% of cases. It is responsible for the transport of phospholipids through the hepatocytes'

canalicular membranes (NIRMALADEVI, 2019; Soria-Jasso et al., 2019). Many mutations have been seen over the years affecting the bile acid excretion levels. Up to 10 different MDR3 mutations have been identified, and any one of these mutations may result in loss of function and raise bile acid levels (Ayyash et al., 2021; Ferrando et al., 2020; Khunweeraphong and Kuchler, 2021; Yang et al., 2023). There have been associations with progressive familial intrahepatic cholestasis as it has a similar gene mutation (Awanti Jr et al., 2023; Bosma et al., 2020). Therefore, a thorough and detailed family history of a patient with intrahepatic cholestasis of pregnancy is crucial. This includes checking for any personal or family history of IHCP, gallstones, or cholestasis with the use of the oral contraceptive pill (OCP).

Genetic predisposition can lead to a heightened response to estrogen (White, 2020). Cholestasis can develop from OCPs that include estrogen because estrogen is known to have a role in its development (Shao et al., 2021). Compared to the non-pregnant condition, the levels of all types of steroid hormones, including estrogen, progesterone, and corticosteroids, rise to more than1000 times during the third trimester of pregnancy (Soria-Jasso et al., 2019). These hormones prevent the excretion of bile salts by interfering with the hepatocyte export pump, causing cholestasis (NIRMALADEVI, 2019). Another way that sex hormones interact is by linking elevated levels of sex hormones to poor sulfation. Sulfated progesterone metabolites can potentially overwhelm the hepatic transport systems for biliary excretion (Majsterek et al., 2022; NIRMALADEVI, 2019).

With subsequent pregnancies and multiple gestations, there is an increase in the estrogen levels in the maternal body, leading to a significant risk of intrahepatic cholestasis.

Many drugs have been tried for the treatment of IHCP, but none is adequate. Ursodeoxycholic acid has shown promising results as an effective drug for the treatment of IHCP. It has also been shown to improve the symptoms and liver biochemistry in other cholestatic diseases. The exact mechanism of this drug is still unclear. However, it acts as a critical trans locator or transporter protein, resulting in increased excretion of bile salts from the liver and reducing the risk to the fetus. Taurocholic and ursodeoxycholic are two bile acid salts identified in recent investigations as specifically being increased in ICP. It's worth noting that ursodeoxycholic acid (UCDA), currently the primary pharmaceutical remedy, can help reduce bile acid levels. A dose of 15-25mg/kg/day in divided doses is typically administered. The objective of this study was to investigate the maternal and fetal outcomes in women who are being treated with Ursodeoxycholic acid (UDCA) for intrahepatic cholestasis of pregnancy (IHCP).).

Methodology

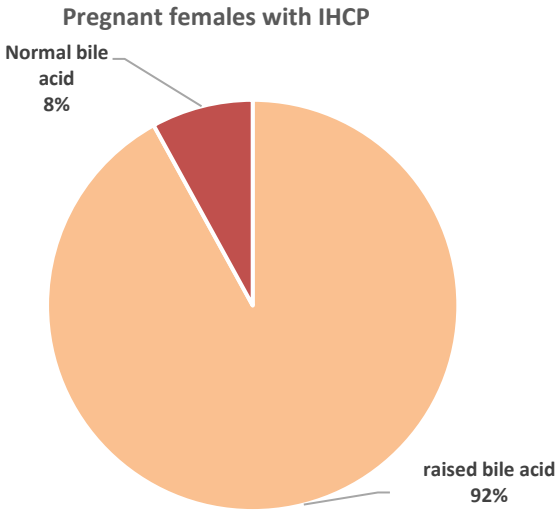
As part of an observational cross-sectional study, 75 pregnant women with diagnosed Intrahepatic Cholestasis of Pregnancy (IHCP) were enrolled at Fatima Memorial Hospital in Lahore after providing informed consent over a period of one year, from January 21st, 2021, to January 20th, 2022. The study was conducted in collaboration between the Department of Gastroenterology and the Department of Obstetrics and Gynecology. The investigators analyzed the patient's symptoms, risk factors, and clinical and laboratory parameters at the time of presentation and after starting treatment with Urso Deoxycholic Acid (UDCA). Patients were followed up until delivery, and their modes of delivery, maternal outcome of itching, and fetal outcome in terms of Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score were also noted. The inclusion criteria for the study were pregnant females with deranged liver function tests and itching, pregnant females with raised bile acid levels, single or twin pregnancies with no known fetal anomaly, and a gestational amenorrhea of the 2nd and 3rd trimester. The exclusion criteria were pregnant females with deranged liver function tests with causes other than IHCP and any history of allergy to UDCA.

The data was analyzed using SPSS software, and the improvement of symptoms was compared before and after treatment with UDCA. The primary outcome was an improvement in symptoms clinical and laboratory parameters from the time of diagnosis of IHCP in these women until their delivery.

Results

Serum Bile acid level was significantly raised in 92% of pregnant women with IHCP, and the use of ursodeoxycholic acid caused complete resolution of itching in 57.7% of patients, reduced to mild in 40.4% and moderate itching in 1.9% of patients. A marked reduction in alkaline phosphatase (Mean 30IU) and ALT (Mean 29IU) after treatment of UDCA was seen, with p-values of 0.001 and 0.004, respectively. The range of dose required for UDCA was 10-25mg/kg/day.

Among the patients, 36.5% had a positive family history of IHCP, 33% had a history of IHCP in previous pregnancies, and 16% had twin pregnancies. The incidence of early delivery was seen in 98%, with a mean gestational age of 36.4 weeks. Among these early deliveries, 8% had SVD, and 92% had C-sections. The indications of delivery were intractable itching and no improvement in LFTS in 15%, PROM and fetal distress in 21%, failed induction in 31%, previous cesarean in 23%, and other reasons in 10%. The 99% of babies had good APGAR scores and no morbidity but 1% mortality due to severe IHCP in the mother



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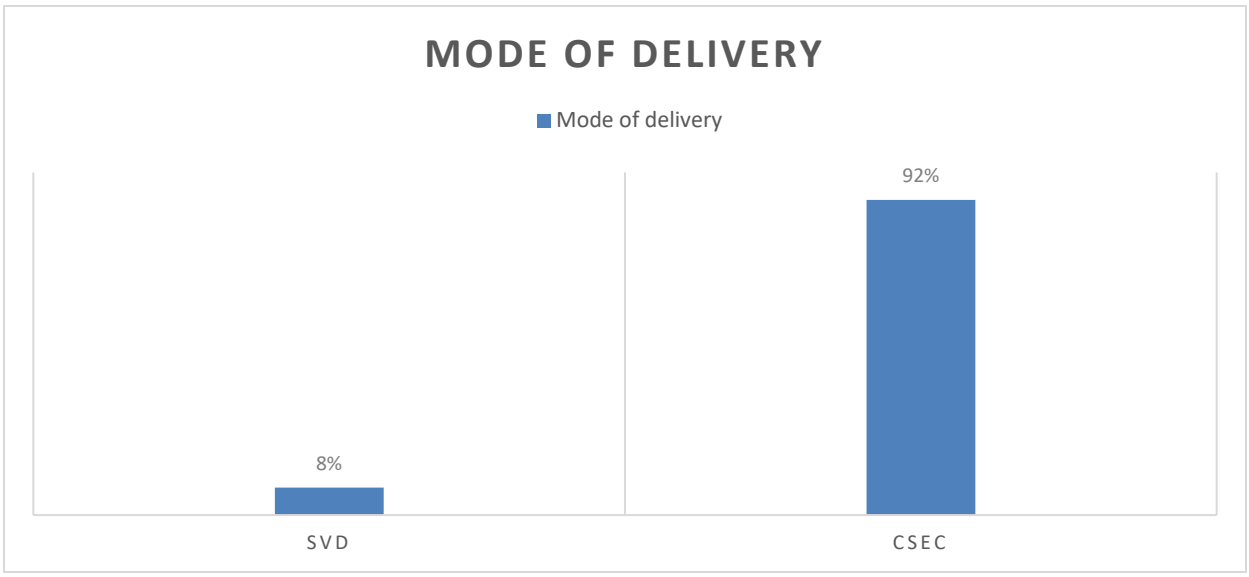

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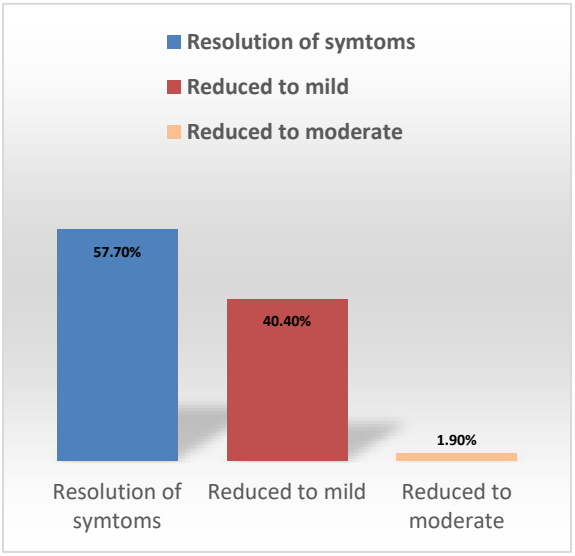

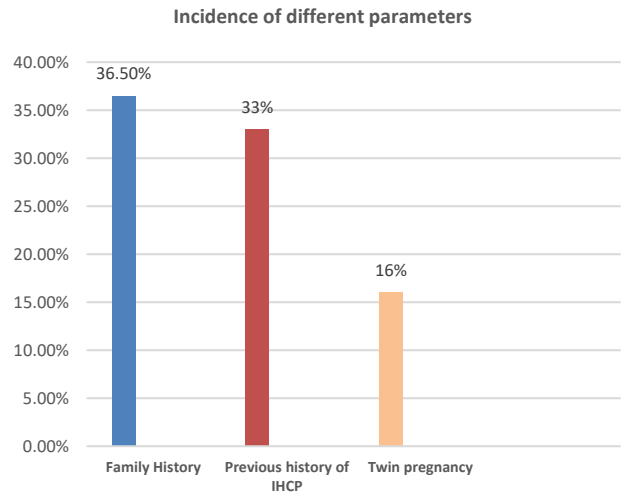

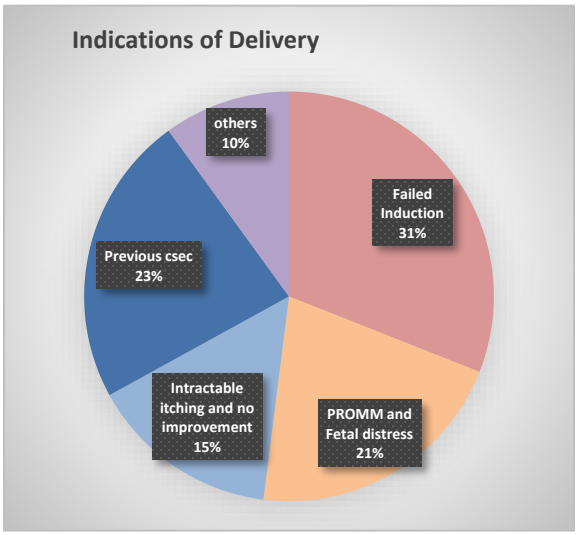

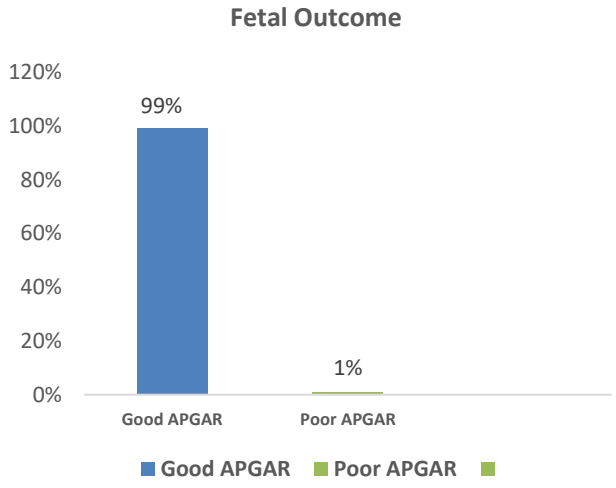

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Discussion

Intrahepatic cholestasis of pregnancy (IHCP) is a condition that primarily manifests in the late second or early third trimester and is characterized by hormonally driven cholestasis. This study aimed to evaluate the maternal and fetal outcomes in pregnant women with IHCP treated with Ursodeoxycholic acid (UDCA). Our findings revealed a significant improvement in clinical and laboratory parameters following UDCA treatment.

The study showed that ursodeoxycholic acid had demonstrated beneficial results in improving the subjective and clinical condition of the patient, along with a marked decrease in the laboratory parameters, which included raised alkaline phosphatase, bile acid levels, and transaminases. The required dosage to alleviate the symptoms ranged from 10-25mg/kg/day. Only a few patients required higher doses to meet the respective results. The factors observed to be playing a role in the development of IHCP included family history and personal history of IHCP in previous pregnancies and twin pregnancies. There was an increased incidence of early deliveries, which were dependent on the fetal conditions, i.e., fetal distress and premature rupture of membranes, which implies that early deliveries should be advised to avoid the development of fetal distress. There was no maternal mortality reported; however, fetal mortality was noted, which was likely due to the late presentation of the patient to the hospital, late diagnosis, and subsequently, the management was also delayed, and at that later hour, even urso cannot be of much benefit. So, the timely initiation of ursodeoxycholic acid is of utmost importance.

Conclusion

In our part of the world, resources are limited, and early diagnosis of liver diseases in pregnancy is difficult due to multiple factors. The delay in diagnosis and management can lead to the possibility of worse outcomes in fetuses. The early treatment with ursodeoxycholic acid and premature delivery, either through spontaneous vaginal delivery or through cesarean section, has been shown to help in improving fetal outcomes. Has a significant response to UDCA with marked improvement in physical and laboratory parameters. There is still limited data, and much more extensive studies are required to indicate the various maternal and fetal complications. An early delivery has a better maternal and fetal outcome.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

Approved by the department Concerned.

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors contribution

• *SAHERISH RIAZ QURESHI*	*Review of Literature, Drafting article*
• *AFTAB HAIDER ALVI*	*Conception of Study, Development of Research Methodology Design, Study Design, Review of Literature, Drafting article, Review of manuscript, final approval of manuscript*
• *AIJAZ ZEESHAN KHAN CHACHAR*	*Conception of Study, Final approval of manuscript*
• *MUHAMMAD SOHAIB*	*Data entry and Data analysis, drafting article*
• *SAJJAD ALI*	*Study Design, Review of Literature*
• *MUHAMMAD ABDULLAH*	*Study Design, Data collection, and data analysis*

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