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ORIGINAL ARTICLE

Pregnancy Outcomes with Intrahepatic Cholestasis

GHIAS UL HASSAN[1], IRAM INAM[2], SAADIA SAJJAD[3]
[1]Assistant Professor, Department of Gastroenterology, PGMI/LGH Lahore, Pakistan
[2]Associate Professor, Department of Gynae/Obs, Continental Medical College Lahore, Pakistan
[3]Associate Professor Department Physiology, Abu Ammara Medical & Dental College Lahore
Correspondence to: Ghias ul Hassan, Email: ghiasulhassan@gmail.com, Cell: 0345-4040302

ABSTRACT

Introduction: ICP is a reversible rare disorder prevailing in 2% of pregnancies resulting in debilitating feto-maternal consequences. Maternal problems resolves soon after delivery but fetal complications result in multiple deteriorations. Present study was undertaken to assess the pregnancy outcomes with ICP on both mother and fetus.

Methodology: A prospective study design was used and study was conducted in tertiary health care sector in department of obstetrics and gynecology for period of 2 years. 80 mothers with history of pruritus, aminotransferase levels > 30 IU/L and alkaline phosphatase > 300 IU/L were included in this study. Pregnancies with other liver disorders were excluded. Study was conducted after institutional approval. Data was analyzed using SPSS version 23.0 and descriptive statistics were used to display the data in the form of frequency and percentages.

Results: ICP accounted for many adverse feto-maternal outcomes. Results show sleep disturbance in 68.75%, PROM in 73%, risk of PPH 10% and 75.5% births were through operative method attributable to ICP. ICP caused fetus distress in 20% cases, MSL in 23.75% of babies, preterm birth (25%) and LBW babies (18.75%), rate of NICU admission (18.75%) and still birth revealed in 2.5% cases in this study.

Conclusion: Present study depict the ill effects of ICP on both mother and fetus. Maternal effects are reversible but fetal effect cause permanent impairment for rest of fetus life. There is need for vigilant monitoring of the pregnant women affected with ICP to avoid such painful events.

Keywords: Pregnancy, Intrahepatic, Cholestasis, Outcomes.

INTRODUCTION

Intrahepatic cholestasis is a reversible rare disorder prevailing in 2% of pregnancies. Disease usually affects in late second and third trimester of pregnancy. Liver is the main organ involved in intrahepatic cholestasis[1]. Disease progress slowly and manifest as pruritus in the third trimester of pregnancy. Maternal problems resolves soon after delivery but fetal complications result in multiple deteriorations[2]. Many factors are involved in pathogenesis of intrahepatic cholestasis. Hormonal levels are raised due to pregnancy and cause worsening condition. Estrogen is the key factor involved in the development of disease[3]. Estrogen hormone levels are responsible for reducing the expression of bile acid receptors and decreasing the sensitivity of binding proteins. Bile acids levels build up in liver due to obstruction in flow of bile[4].

Intrahepatic cholestasis was first diagnosed as a case of recurrent jaundice by Ahlfeld in 1883[5]. The case was recovered soon after birth but caused child complications. Pruritus was a clinical manifestation in third trimester of pregnancy with high revival rate in consequent pregnancies[6]. Genetic and environmental factor along with hormonal effects are responsible for etiology of ICP. In pregnancy, there is elevation in reproductive hormones that affect liver cells liable for bile acids flow. As a result of this deterioration, bile acid levels buildup in liver and lead to pruritus on palm and sole of women feet[7]. Effect on fetus are devastating ranging from miscarriages to IUD. Still birth, RDS, meconium passage, fetal asphyxia, preterm delivery and fetal loss are the frequent complications of ICP. Pathogenesis of fetal complications is still unknown, bile acid levels are responsible in causation of fetal complication[8].

Incidence rate of ICP varies across countries based on ethnicity and geographic variations. In Pakistan, recent data suggest incidence rate of 3.1%[9]. In Chile, peaked incidence rate of 16% is reported attributable to various factors, seasonal versus intake of vitamins and minerals[10]. As, advance studies depict the involvement of low selenium intake and vitamin D in causation of ICP[11].

Diagnosis of ICP is based on pruritus, altered liver function test and serum bile acid levels. These symptoms are associated with bile flow obstruction due to disrupted hepatocyte transport mechanism[12]. Increased bile acid levels lead to fetal complications such as distress, premature birth and intrauterine death. Abnormalities are ascribed to trans-placental transport of bile acids and toxins[13]. That is deteriorated in ICP compared to normal pregnancy. In ICP increased transfer of bile acid from mother to fetus is accountable for fetus complexities. Accumulation of bile acid levels in fetus lead to devastating effects on fetus wellbeing[14]. Maternal symptoms subside with the use of Ursodeoxycholic acid although its mechanism is unknown but usage is beneficial in treating pruritus[15]. ICP is associated with diverse feto-maternal outcomes. Present study was undertaken to assess the pregnancy outcomes with ICP on both mother and fetus.

METHODOLOGY

A prospective study design was used to see the feto-maternal outcomes associated with ICP. Study was conducted in tertiary health care sector in department of obstetrics and gynecology for period of 2 years, June 2018 to May 2020. Approximately thousands of deliveries were conducted during this period but only 80 mothers with history of pruritus, aminotransferase levels > 30 IU/L and alkaline phosphatase > 300 IU/L were included in this study. Pregnancies with other liver disorders were excluded. Study was conducted after institutional approval. Participants were informed regarding study purpose and informed consent was taken.

In this study, Liver function test were repeated on weekly basis and Ursodeoxycholic acid 300-1200 mg/day was given in divided doses to the diagnosed cases for rest of pregnancy period. These cases were followed during labour and delivery till postpartum and perinatal period. Women were followed for 6 week after delivery to see the further complications and liver enzyme levels were monitored during this period.

Outcomes of present study were maternal and fetal complications. Maternal outcomes associated with this study were sleep disturbance due to pruritus, abnormal coagulation profile, dyslipidemia, PROM, and PPH. Fetal outcomes in present study were fetal distress, Meconium stained liquor, preterm birth, LBW, NICU admission and perinatal death.

Data was analyzed using SPSS version 23.0 and descriptive statistics were used to display the data in the form of frequency and percentages.

RESULTS

A total of 80 pregnant women participated in this study. Maternal characteristics are shown in table#1.

Table 1: Demographics of the Study Participants.

Characteristics	Frequency	Percentage
Age of Participants in Years		
<20 years	11	13.75%
21-25	36	45%
26-30	28	35%
31-35	3	3.75%
>35 years	2	2.5%
Gestational age		
<28 years	3	3.75%
28-32	13	16.25%
32-36	54	67.5%
>36	10	12.5%

Above mentioned table shows that mostly participants belong to age group 21-25 years. Gestational age of mother shows that most women were in their 3rd trimester of pregnancy. As ICP starts in late second and third trimester, results in this study also depict that 54 (67.5%) women were in their third trimester of pregnancy.

Table 2: Maternal outcomes with ICP.

Outcomes	Frequency	Percentage
Sleep disturbance	55	68.75%
Dyslipidemia	28	35%
Deranged coagulation profile	27	33.33%
PROM	58	73%
PPH	8	10%
Operative Delivery	60	75.5%

Maternal outcomes in association with ICP show that sleep disturbance was present in 55 (68.75%) pregnant women out of 80. Sleep disturbance is mainly associated with pruritus. Also, table#2 shows that 28 (35%) women had dyslipidemia, 27(33.33%) had deranged coagulation profile. History of PROM was revealed in 58 (73%) studied women. Other maternal outcomes like PPH and operative delivery was found in 8(10%) and 60(75.5%) study participants depicted in above mentioned table#2. In this study maternal outcomes like sleep disturbances, dyslipidemia, pruritus etc. were resolved as participants were followed for 6 weeks after delivery.

Table 3: Fetus outcomes with ICP.

Outcomes	Frequency	Percentage
Fetal distress	16	20%
Meconium stained liquor	19	23.75%
Preterm birth	20	25%
LBW	15	18.75%
NICU admission	15	18.75%
IUD/Still birth	2	2.5%

Fetus outcomes show that fetal distress was present in 16(20%) and MSL found in 19 (23.75%) of cases. Results of this study show 20 (25%) preterm births and 15(18.75%) LBW babies as fetus outcomes caused by ICP. 15 (18.75%) NICU admissions and 2 (2.5%) cases of IUD were also found in present study shown in above mentioned table#3.

DISCUSSION

ICP is the commonest cause of liver disorders in pregnancy accountable for adverse feto-maternal outcomes. ICP is characterized by pruritus in third trimester of pregnancy that produces an unpleasant sensation. Elevated liver enzyme levels due to cholestasis progress to adverse consequences and worsen the condition further.

Incidence rate of ICP varies across boundaries and ethnicity also affects its distribution. In present study, incidence of ICP is 3% according to findings based on study results. Other studies also calculated the incidence rate of ICP as 3 to 5% depending on geographic variation[16]. These findings are also consistent with a study conducted in Pakistan revealing incidence rate of 3.1%[17]. These variations in incidence rate are attributed to multiple factors like seasonal, environmental, ethnical, eating habits, geographic location etc.

In ICP, pruritus is the chief compliant that cause unpleasant feelings leading to sleep disturbance at night. Pruritus is present on hand and palm of sole mainly and creates a disturbing situation. In this study, sleep disturbance was evident in 68.75% study participants. This ratio is high and predicts adverse maternal outcome associated with ICP. Similarly, a study conducted by LEE et al, depicts that sleep disturbances due to pruritus cast ill impact and worsen the women health[18.]

Results of the current study show that history of PROM was present in 73% of the participants. Although no direct relationship of ICP with PROM is evident but may be certain transport receptors are responsible for this outcome. Other studies also show similar results and cases of PROM was encountered in study population[19].

ICP is also associated with PPH and operative deliveries. Risk of ICP provoke the incidence of PPH and operative births in pregnant women. In our study, risk of PPH is 10% and 75.5% births were through operative method attributing to ICP. These findings are consistent with other studies revealing the cases of PPH and C-Section deliveries due to ICP[20]. Other maternal outcomes in this study, dyslipidemia and deranged coagulation profile was also noticed in 35% and 33.33% study participants. Moreover, studies also show similar incidence of maternal outcomes[21].

Fetal outcomes are also correlated with ICP. In pregnancies having the risk of ICP, many hostile events threaten the fetus life. In this study, results show that ICP caused fetus distress in 20% cases. Fetal distress is an accentuating state that endanger the life. Similarly, a study by Williamson et al, showed fetal distress as chief compliant ascribed to ICP[22].

In the present study, MSL was obvious in 23.75% of babies. This incidence was high and compromise the fetal life through many adverse consequences. A study by Tolunay et al, provide ample evidence regarding risk of MSL in mother with ICP[23]. Other fetal outcomes noticeable in our study were preterm birth (25%) and LBW babies (18.75%). Preterm birth are due to transport of bile acid levels through placental transport receptors. Similarly, LBW is also the result of ICP during pregnancy. A study by Zhang et al, show the positive effects of Ursodeoxycholic acid in treating ICP during pregnancy and prevent the hostile fetal outcomes[24].

Risk of ICP is also a factor for increased ICU admission and still birth in newborns. In our study, rate of NICU admission was 18.75% cases. Some of these newborns recovered early than others. Still birth was revealed in 2.5% cases in this study. These findings are similar to other studies conducted in ICP affected pregnant women where fetal outcomes were comparable to our study[25].

CONCLUSION

Present study depict the ill effects of ICP on both mother and fetus. Maternal outcomes are reversible but fetal effect cause permanent impairment for rest of fetus life. Prematurity, LBW and NICU admission threaten the fetal life expectancy and provoke destressing condition. Furthermore, babies with LBW contract multiple infectious and other disorders later in life, if survived. There is need for vigilant monitoring of the pregnant women affected with ICP to avoid such painful events. Awareness regarding ICP should be raised to limit the chances of hostile fetal outcomes. Vigorous antenatal management of pregnancies contracted with ICP is a key to enhance surveillance rate.

Authors Contribution

GH conceived, designed and did statistical analysis
II did data collection & manuscript writing
SS did review and final editing of manuscript

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REFERENCES

1. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstetrics & Gynecology. 1999 Aug 1;94(2):189-93.
2. SAVONIUS H, RIIKONEN S, GYLLING H, Haukkamaa M. Pregnancy outcome with intrahepatic cholestasis. Acta obstetricia et gynecologica Scandinavica. 2000 Jan 1;79(4):323-5.
3. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: review of six national and regional guidelines. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Dec 1;231:180-7.
4. Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Ilio C, Chambers J, Kohari K, Bacq Y, Bozkurt N, Brun-Furrer R, Bull L. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. The Lancet. 2019 Mar 2;393(10174):899-909.
5. Chappell LC, Bell JL, Smith A, Linsell L, Juszczak E, Dixon PH, Chambers J, Hunter R, Dorling J, Williamson C, Thornton JG. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. The Lancet. 2019 Sep 7;394(10201):849-60.
6. Feng C, Li WJ, He RH, Sun XW, Wang G, Wang LQ. Impacts of different methods of conception on the perinatal outcome of intrahepatic cholestasis of pregnancy in twin pregnancies. Scientific Reports. 2018 Mar 5;8(1):1-8.
7. Walker KF, Chappell LC, Hague WM, Middleton P, Thornton JG. Pharmacological interventions for treating intrahepatic cholestasis of pregnancy. Cochrane Database of Systematic Reviews. 2020(7).
8. Arthuis C, Diguisto C, Lorphelin H, Dochez V, Simon E, Perrotin F, Winer N. Perinatal outcomes of intrahepatic cholestasis during pregnancy: An 8-year case-control study. PloS one. 2020 Feb 19;15(2):e0228213.
9. Ovadia C, Sajous J, Seed PT, Patel K, Williamson NJ, Attilakos G, Azzaroli F, Bacq Y, Batsry L, Broom K, Brun-Furrer R. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. The Lancet Gastroenterology & Hepatology. 2021 Jul 1;6(7):547-58.
10. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic cholestasis of pregnancy: a review of diagnosis and management. Obstetrical & gynecological survey. 2018 Feb 1;73(2):103-9.
11. Batsry L, Zloto K, Kalter A, Baum M, Mazaki-Tovi S, Yinon Y. Perinatal outcomes of intrahepatic cholestasis of pregnancy in twin versus singleton pregnancies: is plurality associated with adverse outcomes?. Archives of gynecology and obstetrics. 2019 Oct;300(4):881-7.
12. Gao XX, Ye MY, Liu Y, Li JY, Li L, Chen W, Lu X, Nie G, Chen YH. Prevalence and risk factors of intrahepatic cholestasis of pregnancy in a Chinese population. Scientific Reports. 2020 Oct 1;10(1):1-7.
13. Vasavan T, Deepak S, Jayawardane IA, Lucchini M, Martin C, Geenes V, Yang J, Lövgren-Sandblom A, Seed PT, Chambers J, Stone S. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. Journal of hepatology. 2021 May 1;74(5):1087-96.
14. Mor M, Shmueli A, Krispin E, Bardin R, Sneh-Arbib O, Braun M, Arbib N, Hadar E. Intrahepatic cholestasis of pregnancy as a risk factor for preeclampsia. Archives of gynecology and obstetrics. 2020 Mar;301(3):655-64.
15. Di Mascio D, Quist-Nelson J, Riegel M, George B, Saccone G, Brun R, Haslinger C, Herrera C, Kawakita T, Lee RH, Benedetti Panici P. Perinatal death by bile acid levels in intrahepatic cholestasis of pregnancy: a systematic review. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Nov 2;34(21):3614-22.
16. Manna LB, Ovadia C, Lövgren-Sandblom A, Chambers J, Begum S, Seed P, Walker I, Chappell LC, Marschall HU, Williamson C. Enzymatic quantification of total serum bile acids as a monitoring strategy for women with intrahepatic cholestasis of pregnancy receiving ursodeoxycholic acid treatment: a cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2019 Dec;126(13):1633-40.
17. Liu C, Gao J, Liu J, Wang X, He J, Sun J, Liu X, Liao S. Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes and preeclampsia. Annals of Translational Medicine. 2020 Dec;8(23).
18. Lee RH, Greenberg M, Metz TD, Pettker CM, Society for Maternal-Fetal Medicine (SMFM. Society for maternal-fetal medicine consult series# 53: intrahepatic cholestasis of pregnancy: replaces consult# 13, April 2011. American Journal of Obstetrics and Gynecology. 2021 Feb 1;224(2):B2-9.
19. Smith DD, Rood KM. Intrahepatic cholestasis of pregnancy. Clinical obstetrics and gynecology. 2020 Mar 1;63(1):134-51.
20. Piechota J, Jelski W. Intrahepatic cholestasis in pregnancy: review of the literature. Journal of Clinical Medicine. 2020 May;9(5):1361.
21. Roediger R, Fleckenstein J. Intrahepatic Cholestasis of Pregnancy: Natural History and Current Management. InSeminars in Liver Disease 2021 Jan (Vol. 41, No. 01, pp. 103-108). Thieme Medical Publishers, Inc.
22. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstetrics & Gynecology. 2014 Jul 1;124(1):120-33.
23. Tolunay HE, Kahraman NÇ, Varlı EN, Ergani SY, Obut M, Çelen Ş, Çağlar AT, Üstün YE. First-trimester aspartate aminotransferase to platelet ratio index in predicting intrahepatic cholestasis in pregnancy and its relationship with bile acids: A pilot study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021 Jan 1;256:114-7.
24. Zhang Q, Xu Y, Gong Y, Liu X. Perinatal Outcomes Of Ursodeoxycholic Acid Treatment In Twin Pregnancies With Intrahepatic Cholestasis: A Five-Year Retrospective Cohort Study.
25. Huri M, Seravalli V, Lippi C, Tofani L, Galli A, Petraglia F, Di Tommaso M. Intrahepatic Cholestasis of Pregnancy-time to redefine the reference range of total serum bile acids: a cross-sectional study. BJOG: An International Journal of Obstetrics & Gynaecology. 2022 Feb 10.