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INTRAHEPATIC CHOLESTASIS OF PREGNANCY & ADVERSE PERINATAL OUTCOMES

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ABSTRACT

Introduction: Pregnancy can come up with intrahepatic cholestasis in third trimester attributed by any of the several medical conditions that affects liver. Intrahepatic cholestasis is a functional disorder involving hepatic parenchymal cells and intrahepatic bile ducts. It can lead to adverse fetal outcomes in cases of prolonged diagnosis and delayed treatment. **Objective:** The current study was done to find correlation amongst effects of intrahepatic cholestasis during pregnancy, health of fetus and pregnancy carrier and health of neonates once delivered. **Methods:** It was performed through quantitative examinations by accumulating data via questionnaires and analyzing it using SPSS statistical software at Royal Medical Services Hospital, Jordan for three years. 100 cholestasis pregnant females out of 12,000 women were diagnosed and studied. **Results:** Incidence rates of IHC in selected cohort was found to be 0.83% . Study indicated that IHC/obstetric cholestasis is major factor that is governed by type of pregnancy and number of deliveries having a history of liver disease. Studying fetal outcomes did not yield any connection with respective factors that were considered. Distinct processes of analysis did not give any significant results.**Conclusion:** Future studies are recommended for affirming any correlations for fetal outcome by accounting novel factors as subjects here are variables getting affected with masked factors. It can be concluded from the obtained results that obstetric cholestasis (OC) can be treated or avoided by administering concomitant and related medical conditions.

KEYWORDS: Intrahepatic cholestasis, pregnancy, obstetric cholestasis, fetal outcome.

INTRODUCTION

Intrahepatic cholestasis (IHC) is the most common functional liver disorder involving hepatic parenchymal cells and intrahepatic bile ducts and distinguished as extralobular or intralobular.[1] Former cholestasis is a consequence of intrahepatic bile ducts while latter is a derivative of hepatic parenchymal cells & transporter molecules. Blood carries bile components, bile acids and bilirubin, that are retained during cholestasis.[2] Peculiar liver abnormalities that occur during pregnancy highlighted by unsettled liver capacity increasing hepatic bile acids levels to more or equal to 10 micromol/l is referred as obstetric cholestasis (OS).[1] During this clinical condition, enzyme serum aminotransaminases levels rise two to ten times depending on severity of condition. This increase can result earlier or can follow when serum bile becomes corrosive usually in addition to rise in bilirubin levels. Placental isoform accumulates in huge measure that results in constrained analytic worth raising soluble phosphatase levels.[2]

Co-relationship between intrahepatic cholestasis of pregnancy and adverse fatal outcome

The significantly recognized clinical manifestation involves pruritus without rashes that are progressively set apart on sole and palm areas. Pruritus is an indication of accumulation of excessive bile acid in hepatic periportal region. Signs begin appearing with progression of pregnancy in third trimester of pregnancy while getting serious and eventually subsides post -delivery. Severity is marked by biochemical markers and side effects in third trimester that begin to become normal within fourteen days of delivery.[3] Etiology of this condition is multi factorial that varies with habitat and ethnicities being existent globally.[4] IHC is reversible causing almost no harm to women but can have adversities in fetal outcomes. These include preterm deliveries, bradycardia in fetus, meconium staining the amniotic fluid, distress in fetus and fetal morbidity.[5] Despite of not knowing exact factors behind adverse fetal outcomes, it is evident that bile acids levels in serum were found higher i.e. more than 40 micromol/l.[5]

Post term prognosis and increase risk of intrauterine fetal death and stillbirth

Babies born as stillbirths is a concern with 1/3rd babies born in United Kingdom as stillbirths.[6] Stillbirth babies are born post 37 weeks or even less and weight is not found dependent on intrapartum and antenatal care.[6,7] It remains unidentifiable during pregnancy crushing guardians with its splendid quality.[8,9] Data analysis for intrauterine fetal deaths from intrahepatic cholestasis requires broader comprehension covering maximum number of variables, manifesting datasets of samples for features like gestational age.[8,9,10] It has been studied earlier that occurrence of IHC elevates frequency of delayed preterm deliveries. Chances of still births elevates with expanded tenure of incubation despite of keeping pregnant females under supervision and it expands after 41 weeks' gestation.[10,11,12,13] Before 41 weeks' gestation period, rate of such cases reduces to 1/3rd but delivery is a random chance as no special examination occurs unless presence of clinical signs is seen.[13] Term pregnancies occur in certain cases because of fear of antagonistic neonatal outcomes before 41st week of pregnancy.[6,8,9] Howsoever, 1 in every 3 stillbirths are occurring prior 41 weeks of incubation period.[14,15] It can be monitored by fetal size and consistency as per reference of gestational week for examining possibility of still birth.[16,17,18] Evaluation of mortality rates within neonates is not enough for clinical experts to provide the information about cases and causes.[17,19,20]

The statistical research was done with an aim of searching the correlation between effect of having intrahepatic cholestasis on pregnancy, maternal & fetal health and neonatal health post- delivery. Investigating major issues involved identifying relationship between intrahepatic cholestasis during pregnancy and its influence for adverse fetal outcomes. Post term prognosis and elevated probabilities for risk of intra uterine fetal morbidity resulting in still births was also analyzed.

METHODOLOGY

The subjects and data were collected at Royal Medical Services Hospital in Jordan. The study spanned through a course of three years from April 2017 to April 2020. The current examination is a quantitative examination performed with an aim to solve the issues and objectives mentioned. Surveys were prepared enquiring mothers, nurses and secondary resources in order to collect datasets that are related to cholestasis that occur during maternity. Subsequently, several aspects were derived that influence fetal outcomes during occurrence of intrahepatic cholestasis during pregnancy

Subjects & selection criteria

More than 12,000 pregnant females participated in data collection. Patients were examined and confirmed for falling in selection criteria by five medical specialists. 100 patients with intrahepatic cholestasis of pregnancy were classified on reporting clinical symptoms with pruritis without rashes on palms and soles in addition to laboratory findings.

Statistical analyses

The collected data was organized in charts format and several multiple characteristics were correlated. Entire information was then entered and analyzed using SPSS statistical software.

RESULTS

Demographic data analysis

Pregnant females that were identified and statistical/ demographic data collected through surveys were recorded and can be referred in table 1. Primarily out of all candidates, women falling in age range of 20 – 30 years were found mostly suffering followed by those in range of 30-40 years. The most susceptible age group for IHC being 20 – 40 years. Education data was referred next where most sufferers had education till secondary school, then Bachelor's followed by others. Data on working status did not show significant variation indicating unemployed and dynamically working females making 75% cases while office goers were ~25% cases. 100 female subjects were identified with intrahepatic cholestasis where 50% females were healthy while rest were either suffering with acute medical condition, chronic medical condition or both. Activeness of expecting mothers determine their health and fetal health. It also governs the kind of delivery procedure that a female will go through at time of delivery. IHC occurrence was still found to be equally distributed amongst pregnant females with low and highly active lifestyles. Following section in table 1 describes subject's distribution depending on type of pregnancy i.e. primigravida or multigravida. Primigravida are mothers delivering their first baby and multigravida are mothers having second or more baby. The frequencies were found almost equal for both cases and interestingly as seen in next column, mothers conceived first time were most susceptible for having IHC.

Table 1. Incidences of IHC occurrence based on Age data, educational data, working status, mother health, activity level, pregnancy type, and number of deliveries.

Age Data			Educational Data		
	Frequency	Percent		Frequency	Percent
<20	14	14.0	Uneducated	9	9.0
20-30	46	46.0	Primary school	16	16.0
30-40	29	29.0	Secondary school	30	30.0
>40	11	11.0	Diploma	14	14.0
			Bachelor's degree	20	20.0
			Postgraduate studies	11	11.0
Total	100	100.0	Total	100	100.0
Working Status			**Mother's Health**		
	Frequency	Percent		Frequency	Percent
Unemployed	37	37.0	Healthy	50	50.0
Dynamic work	36	36.0	Having acute medical condition	16	16.0
Office work	27	27.0	Having chronic medical condition	21	21.0
			Having chronic along with acute medical condition	13	13.0
Total	100	100.0	Total	100	100.0
Activity level			**Type of Pregnancy**		
	Frequency	Percent		Frequency	Percent
Low	51	51.0	Primigravida	49	49.0
High	49	49.0	Multigravida	51	51.0
Total	100	100.0	Total	100	100.0

Number of Deliveries		
	Frequency	Percent
1	49	49.0
2	20	20.0
3	11	11.0
4	13	13.0
5 or more	7	7.0
Total	100	100.0

Liver function in pregnancy

Obstetric cholestasis occurs during pregnancy and table 2 presents data of fraction of cases where 80% were found without OC and 20% were detected with OC. It can be correlated to having liver disease before pregnancy that was found in 25% cases and 75% without any such incidence. Names were cross checked to identify same females for formerly described 20% and latter 25%. This information is available in supplementary materials. 76 out of 100 females did not have incidence of OC in earlier pregnancies while 24 females had OC previously.

Table 2. Incidences of Obstetric cholestasis, liver diseases and history of OC in multipara patients in candidates characterized with IHC.

	Incidences of Obstetric Cholestasis		History of Liver Diseases		History of OC in Multipara Patients	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Yes	20	20.0	25	25.0	24	24.0
No	80	80.0	75	75.0	76	76.0
Total	100	100.0	100	100.0	100	100.0

Consequences of Pregnancy and significance of mode of delivery

The consequences of pregnancy differ as each pregnancy case was showing a unique case with the precipitated effects and adversities. The following table 3 is showing the consequences of pregnancy with or without OC. The mode of deliveries was found different in each case of identified pregnancy depending on its concomitant medical conditions and requirements. Table 3 is showing the distribution of mode of deliveries amongst pregnancies.

Table 3 Distribution of consequences of pregnancy & mode of delivery.

Pregnancy Consequences			Mode of Delivery		
	Frequency	**Percent**		**Frequency**	**Percent**
Sleep disturbance	11	11.0	Elective CS	23	23.0
Dyslipidemia	14	14.0	Emergency CS	21	21.0
Deranged coagulation profile	11	11.0	Forceps	7	7.0
PPH	5	5.0	Vaginal Delivery	49	49.0
PROM	6	6.0			
Operative delivery	41	41.0			
Preterm labor spontaneous	4	4.0			
More than one of the above	8	8.0			
Total	100	100.0	Total	100	100.0

Fetal outcomes and their adversities

Fetal outcomes of all the 100 cases were collected and examined appropriately with table 4 showing the results of the fetal outcomes of pregnant mothers that were recruited to be a part of study. Interestingly most cases of 55 fetuses were found to be healthy. Accordingly, the fetus situation was analyzed as it was assumed to be affected with these variables. Table 4 is also showing the data related to fetus health.

Table 4 Distribution of fetal outcomes & fetal situation.

FETAL OUTCOMES			FETAL SITUATION		
	Frequency	**Percent**		**Frequency**	**Percent**
Fetal distress	7	7.0	Healthy and mature	51	51.0
Abnormal CTG	6	6.0	Health with a need of incubator	23	23.0
Meconium stained liquor	6	6.0	Unhealthy and need incubator	19	19.0
LBW	6	6.0	Stillbirth	7	7.0
IUFD or still born	6	6.0			
NICU admission	9	9.0			
Preterm birth	5	5.0			
Healthy Fetus	55	55.0			
Total	100	100.0	Total	100	100.0

Analysis of variance

Post collection of all datasets, association analysis was done with ANOVA to find variables that can make a difference in accordance with variables of interest for this research. OC was made the dependent variable and was studied to find the relationship with the following factors in table 5. Analysis results correctly signified that type of pregnancy, number of deliveries and previously occurring liver diseases in mothers are considerably affecting incidence of OC since p-value was less than 0.05. However, OC incidences in multipara patients were not significantly affecting OC occurrence in data study here. Analysis of fetal situation was done through ANOVA considering fetal outcomes and factors described in table 5. Surprisingly, none of factors considered had any significance towards fetal situation as p value was >0.05 in all cases. Fetal outcomes distribution was studied with mentioned factors and ANOVA showed that none of the factors examined have a relationship with the fetal outcomes, as all of them had a p-value more than 0.05.

Table 5 ANOVA results for OC, fetal situation and fetal outcomes.

Obstetric cholestasis (OC)		Fetal situation		Fetal outcomes	
MODEL	**SIG.**	**MODEL**	**SIG.**	**MODEL**	**SIG.**
Constant	.001	(Constant)	.160	(Constant)	.013
Type of pregnancy	.042	Type of pregnancy	.243	Type of pregnancy	.338
Number of deliveries	.009	Number of deliveries	.172	Number of deliveries	.822
Having liver disease	.000	Having liver disease	.158	Having liver disease	.530
History of OC in multipara patients	.521	History of OC in multipara patients	.854	History of OC in multipara patients	.607
		Obstetric Cholestasis	.128	Obstetric Cholestasis	.477
		Mother health status	.123	Mother health status	.284
		Level of activity	.430	Level of activity	.967

Paired t-test analysis

It is a multiple variable analysis that was performed keeping an invariable constant while varying other factors. It yields the significance of variables on constant factor. Two constants i.e. OC occurrence and fetal situation were correlated with same variables i.e. having liver disease earlier, history of OC in multipara patients, maternal outcomes, mode of delivery, and distribution of fetal outcome.

a. OC with multiple factors of pregnancy

Amongst the study sample, variables were studied in pairs in order to find the extent of association keeping the constant variable of interest as obstetric cholestasis as shown in table 6. As the p-value is less than 0.05, an association was found based on paired t-test analysis. Based on the results, obstetric cholestasis related to having liver disease, history of OC in multipara patients, maternal outcomes, mode of delivery and distribution of fetal outcome. However, fetus situation did not give any association with OC.

Table 6 OC paired t-test.

	95% Confidence Interval of the Difference		
	Lower	Upper	Sig. (2-tailed)
Obstetric Cholestasis – Having liver disease	.00654	.09346	.025
Obstetric Cholestasis – History of OC in multipara patients	.43929	.68071	.000
Obstetric Cholestasis – Maternal outcome	-3.24770-	-2.35230-	.000
Obstetric Cholestasis – Mode of delivery	-1.29195-	-.74805-	.000
Obstetric Cholestasis – Distribution of fetal outcome	-4.87861-	-3.92139-	.000
Obstetric Cholestasis – Fetus situation	-.23842-	.19842	.856

b. Fetal situation

Paired t-test was made to examine fetus situation in correspondence with other variables, and the table 7 is showing the results. Based on paired t-test, history of OC in multipara patients, maternal outcomes, mode of delivery and distribution of fetal outcome had significance on fetal situation as p value was <0.05. Instead having a liver disease had no association with fetal situation with p value >0.05.

Table 7 fetus situation paired t-test.

	95% Confidence Interval of the Difference		Sig. (2-tailed)
	Lower	Upper	
Fetus situation – Having liver disease	-.14709-	.28709	.524
Fetus situation – History of OC in multipara patients	.36861	.79139	.000
Fetus situation – Maternal outcome	-3.23960-	-2.32040-	.000
Fetus situation – Mode of delivery	-1.31151-	-.68849-	.000
Fetus situation – Distribution of fetal outcome	-4.94601-	-3.81399-	.000

Correlation test

Correlation test was made, and Pearson Correlation was calculated for all of the variables, and the presence of any significance with p value <0.05. Only variables which had significance are addressed here. Pearson correlation was found to be significant between education and mode of delivery (-.0207-). OC is related to mother status as Pearson correlation was -0.465- and p-value is 0.000, and it is related to having liver disease with Pearson correlation 0.866 and p-value 0.000. Maternal outcome was related to mode of delivery as Pearson correlation equals to -0.716-. And fetal situation was related to fetal outcome as Pearson correlation equals to -0.288-.

DISCUSSION

Demographic data for IHC candidates and further correlating characteristics

The currently performed biostatistical analysis was carried out by firstly identifying 100 pregnant females out of 12,000 females that suffered from intrahepatic cholestasis. These 100 participants were asked for their consent and data were collected and analyzed through statistical software. Demographic data indicated women falling in age range of 20 to 40 years being mostly affected. It is in consensus with the potent conceivable age for women generally. Interestingly, mothers who were reported healthy constituted 50% proportion of detection with IHC. Factors like working status, pregnancy type and activity level did not pose any significant effect on incidences of IHC. In fact, women undergoing deliveries for first time had higher incidences of detecting with IHC. This demographic data is unique and should be extrapolated further with biochemical, genetic and molecular studies that will aid in

understanding causes of increased susceptibility for certain characteristics.

Identifying interrelationship between IHC and any liver disease history in accordance with pregnancies

Obstetric cholestasis cases were then identified in 20% cases in women with history of liver disease while 80% did not have OC. Candidates with OC also exhibited a history with mild to acute liver disorders and 77% had OC in their earlier pregnancies as well. In our study, the incidence rate of IHC in selected cohort was 0.83%. A limitation to study performed was inability in correlating consequences of pregnancies in distinct cases with incidences of OC and determining any dependence amongst them. However, certain factors were found correlated with IHC or its aftermath such as raised operative deliveries and disturbed lipid & coagulation profiles. Here, data could not indicate occurrence of two consequences simultaneously for a participant. There are studies reported earlier with disturbed lipid profiles in candidates with cholestasis affecting fetal outcome when serum bile acids levels reduce considerably.[27,5,28]

Effects on fetal outcomes due to persisting IHC

Fetal health factors and its outcome were analyzed with similar frequency of 7% for fetal distress and still birth babies. Out of 100, ~ 50% were absolutely healthy and mature fetuses. Howsoever, remaining ~ 45% displayed certain adversities. A limitation of current study was demarcation of affected fetuses biochemically so as to assure these consequences being due to IHC occurrence. The unfavorable results on the fetus are related to IHC of pregnancy incidences that incorporates meconium recolored alcohol, fetal pain, intra uterine passing and preterm birth. Lately, in multiple studies[21,22,23] there is impressive discussion on the degree of the fetal dangers that is implication from existence of obstetric cholestasis. Many studies have been performed earlier in distinct global regions covering range of cohorts indicating adversities resulting from IHC of pregnancy in fetal outcomes. Maternal serum organic chemistry were found to be related to fetal results in numerous studies.[24] In cases when serum bile acids are over 40 micromoles per liter, the complexity of the fetal cases are reported at higher paces[24] or if ladies show jaundice alongside pruritus. These observations propose that fetal hazard with seriousness of the disease are straightforwardly connected and gentle instances of OC has no expanded fetal risk[2] The result of bile level effect on the level of disease severity and seriousness has been examined but frequently serum transaminases levels are examined to build up the determination and degree of disease.[27,28]

The elective delivery at 37 to 38 weeks of growth is generally drilled to avert the expanded danger of still birth at later incubation regardless of IHC seriousness. Anyways, there have been not many reports of gestational weeks at which the intra uterine demise happens.[28] Regardless of whether it is early delivery or medication treatment that averts unfriendly fetal result is as yet a debate. Anti-histamines, Ursodeoxycholic corrosive (UDCA) and topical preparations are usually used in the treatment of IHC in order to decrease the indications of tingling and biochemical variations from the norm. The treatment with vitamin K would diminish the danger of baby blues and intra ventricular discharge of infant.[22] To date there is no examination to consider maternal and neonatal outcome in front of calendar and the delivery upon late term. Notwithstanding what may be normal, potential risk of perinatal and maternal snare in light of work acknowledgment at delivery at early time of pregnancy raises stresses against its potential favorable circumstances. The elective early term delivery is the reason why perinatal complexity which incorporates respiratory dreariness, iatrogenic rashness, birth asphyxia, long standing illnesses and medical clinic affirmation. The instrumental delivery, baby blues discharge, expanded cesarean segment and its results and febrile grimness is incorporated by maternal entanglement.[25,26]

Analyzing dependence of IHC, fetal situation & outcomes on various factors

Results on variance analysis and combination tests are unique findings of this study. IHC incidence is highly dependent on existence of any history of liver disorders and most other factors considered. On the contrary, fetal situation and outcomes did not depend on any of the factors accounted. Markedly IHC and fetal situation were found affected by several factors significantly in paired p-test analysis approving the generalized known notions. It affirmed conclusively that all considerations of liver diseases, IHC persistent in multipara patients, maternal outcome, delivery means and fetal outcome were found to have significant effects on occurrence of obstetric cholestasis and fetal outcome. Maintenance of such condition is dependent on monitoring of bile acid levels constantly during course of pregnancy as IHC is not detrimental but can turn severe if not monitored and treated in due course of time.[25] When monitored regularly, incidences of still births can be avoided due to cholestasis and occurrence can reduce down to that in normal population.[29]

CONCLUSION

In conclusion it can be said that based on the results of our study, having an IHC of pregnancy can be treated or overcome by overcoming the concomitant or the related medical conditions. IHC was found to have significance on fetal situation and outcomes and is affected by history of liver disorders. Treating liver situations appropriately at right times will definitely impact consequences of IHC largely in pregnant females. Pruritus is major symptom for identifying IHC and most maternal candidates do not experience any other significant effects but our study signifies its effects on fetal situation and their outcomes that can range to adversities. The most deleterious being still births and intra uterine fetal morbidity. However, fetal situation did not give any significant dependence on having liver disease previously. The fetal outcomes were

studied as well, and it was found that no relationship was found with the factors studied. But, fetal outcomes and obstetric cholestasis showed dependence highly on all factors studied for their correlation. Majorly, monitoring of biochemical features is essential for keeping condition from attaining severity. Apart from this, IHC did not show serious implications whatsoever on maternal health.

Study performed here with statistical analyses showed interdependence of intrahepatic cholestasis with certain expected factors while ruling out others. More studies are needed in order to confirm the results at molecular and genetic level. Biochemical studies are even suggested further to analyze variables and confirm their dependence on factors studied. In addition, other factors shall also be studied, as these subjects are variables and can be surely getting affected by some more masked factors.

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