Original Research Paper

Volume - 14 | Issue - 06 | June - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

A STUDY TO FIND ASSOCIATION OF VITAMIN D LEVELS WITH SEVERITY OF OBSTETRIC CHOLESTASIS AT TERTIARY LEVEL HOSPITAL IN LUCKNOW, INDIA.

Riya Agrawal*	Senior Resident, Obs and Gynae Department GSVM Medical college Kanpur, UP, India.-208002. *Corresponding Author
Seema Mehrotra	Professor, Obs and Gynae Department KGMU Medical University Lucknow, UP, India.-226003.
Deepak Anand	Associate Professor Health Education, Obs & Gyne Department, G.S.V.M Medical College, Kanpur, U.P, India.-208002.

ABSTRACT **Objective:** to assess association of Vitamin D levels with severity of cholestasis. **Methods:** Pregnant women with obstetric cholestasis and healthy pregnant women were selected as case and control from the antenatal clinics, high risk antenatal wards and labour room. These participants underwent routine antenatal investigations with special investigations of serum vitamin D as hydroxy vitamin D. Results regarding liver function test and vitamin D levels were analysed. **Results:** Statistically, a significant difference was observed in all liver function test parameters. As the severity of cholestasis increased, the level of liver enzymes also increased. Mean bile acid level in mild cholestasis was 21.97±5.01, in moderate cholestasis was 59.87±8.94 and in severe cholestasis was 142.71±9.87. The mean vitamin D levels in the case group was 18.75±11.25 ng/ml and in control was 23.65±11.52 ng/ml and the difference was statistically significant. **Conclusion:** The more the severity of cholestasis, the less the vitamin D level.

KEYWORDS : obstetric, liver enzymes, liver function test, cholestasis, Vitamin D.

INTRODUCTION:

Intrahepatic cholestasis of pregnancy (ICP) is a common hepatic condition of pregnancy that is characterized by unexplained pruritis, increased bile acids, and abnormal liver function tests [1]. Depending on geographic location and ethnicity, prevalence of the disease varies from 1.2% to 1.5% [2].It is a reversible form of cholestasis that occurs primarily in the late second and third trimesters of pregnancy [3,4]. Although it is a benign disease for the mother and usually resolves after delivery, it has been linked to significant and unfavourable perinatal outcomes, including preterm birth, non-reassuring foetal heart tracing, meconium staining of the amniotic fluid, and stillbirth [5]. The pathogenesis of ICP is poorly understood and appears to be multifactorial. Multiple variables, including the cholestatic action of hormones and environmental factors in genetically predisposed pregnant women, contribute to the pathophysiology of the condition [6,7]. Some pregnant women with ICP had mutations in the hepatobiliary transport protein as well. [8] Depending on geographic location and ethnicity, prevalence of the disease varies from 1.2% to 1.5% [2]. The incidence ranges between 1.2 and 1.5 percent in the Asian populations of India and Pakistan. At 27.6 percent, the Araucanos Indians in Chile have the highest prevalence worldwide. [9] Recent evidence suggests that the binding of vitamin D to the vitamin D receptor (VDR) plays a role in hepatobiliary homeostasis and helps regulate bile acid detoxification [10]. VDRs are present in every tissue in the body, including brain, heart, breast, colon and liver, and by binding to the nuclear VDR receptor, Vit D plays a role in regulating bile acid excretion in the liver and intestine. [11]

In recent studies, low levels of Vit D have also been reported in liver diseases such as nonalcoholic fatty liver disease (NAFLD), [12] chronic hepatitis B (CHB), [13] chronic hepatits C (CHC) [14] and primary biliary cirrhosis (PBC), [15] and low levels were found to be associated with severity and treatment response of these diseases. However, there are limited data on serum Vit D status in pregnant women with ICP in the literature. The objective of our study was to to assess association of Vitamin D levels and Severity of Cholestasis.

METHODOLOGY

Objective: To assess association of Vitamin D levels and Severity of obstetric cholestasis.

Study Design And Setting: This study is to estimate Vitamin D levels in women with obstetric cholestasis and normal pregnant women. This study was conducted from year 2021 to 2022 in King George's Medical University, Lucknow, Uttar Pradesh, India.

Participants were selected from the antenatal clinics, high risk antenatal wards and labour room. Informed consent of all participants was taken. All partipants underwent routine antenatal investigations with special investigations of serum vitamin D as hydroxy vitamin D. Total 140 cases were taken under study, 70 Women with Intrahepatic cholestasis in pregnancy and 70 healthy pregnant women.

Inclusion Criteria: Age 18-40 years , patients giving written informed consent

Study Group: women with obstetric cholestasis (diagnosed as per RCOG 2022 classification) [16]

Control group: healthy pregnant women

Exclusion Criteria: Gestational diabetes mellitus, preeclampsia, any parathyroid disorder, chronic systemic disease, multiple gestation and patient not giving consent.

The statistical analysis was done using SPSS (Statistical Package for Social Science) Version 26.0 Statistical Analysis Software.

RESULTS

Table 1. Health Related Parameters Of Study Subjects

Variables	Case n (%)	Control n (%)	Statistical test
Nutritional status (BMI) < 18.5kg/m² 18.5-24.9 25-29.9	 3 (4.3%) 59(84.3%) 8 (11.4%)	 4(5.7%) 59(84.3%) 7(10.0%)	χ^2=0.210; p=0.901
Mean BMI±2 standard deviation	21.91±2.10	22.19±2.08	t value= -0.794 p value=0.428
Gestational Age(weeks) 34-36 36-38 >38	 42(60.0%) 22(31.43%) 6(8.57%)	 25(35.71%) 31(44.29%) 14(20.0%)	χ^2 =9.042 p=0.0109
Mean gestational age ±2 standard deviation	35.62±3.20	37.59±2.86	t=3.840 p=0.0002
Parity Nullipara Primipara Multipara	 36(60.0%) 30(60.0%) 4(60.0%)	 49(60.0%) 19(60.0%) 2(60.0%)	χ^2=5.124; p=0.077
Cholestasis history No history H/o cholestasis	 62(88.57%) 8(11.43%)	 70(100.0%) 0(0.0%)	χ^2 =8.485 p=0.0036

Table no.1 shows that majority of the women in the case and control group i.e. 84.3% each had normal BMI, followed by overweight. Statistically, a non-significant difference was observed in the nutritional status and mean BMI of both groups. The majority of the women had a gestational age of 34-36 weeks, in cases i.e. 60.00%, followed by 36-38 weeks i.e. 31.43%. However, in the control group majority of the patients had a gestational age between 36-38 weeks i.e. 44.29% followed by 34-36 weeks i.e. 35.71%. Statistically, a significant difference was observed in gestational age of case and

control. The majority of the women in case and control group i.e.70.0% and 51.4% respectively were nulliparous, followed by primiparous. Statistically, a non-significant difference was observed in the parity of enrolled women among groups. Statistically, a significant difference was observed in the history of cholestasis in enrolled women among groups.

Table 2. Liver Function Test Of Pregnant Women Enrolled In Case And Control Groups

LFT	CASE [N=70]		CONTROL [N=70]		P-VALUE	
	Mean	SD	Mean	SD	't'	'p'
S. BILIRUBIN	0.61	0.27	0.46	0.51	2.175	0.0313*
AST	194.83	70.16	47.92	22.40	16.69	<0.0001*
ALT	202.75	81.62	49.88	23.56	15.06	<0.0001*
SAP	487.89	188.78	159.86	163.85	10.98	<0.0001*
LDH	209.47	51.48	112.72	55.48	10.70	<0.0001*

Table no.2 shows that in the cases group, the LFT were elevated compared to the controls group. Statistically, a significant difference was observed in all LFT parameters.

Table 3: Level Of Liver Enzymes In Pregnant Women Enrolled In The Case Group According To The Cholestasis Severity

Investigation	Mild Cholestasis (19-40mol/L)	Moderate Cholestasis (40-99mol/L)	Severe Cholestasis (≥100mol/L)	ANOVA P-Value
	MEAN±SD	MEAN±SD	MEAN±SD	
S.Bilirubin (µmol/L)	0.59±0.21	0.61±0.24	0.71±0.25	F=9.870 P<0.0001*
AST (IU/L)	42.35±49.64	116.81±82.10	228.05±151.23	F=46.16 P<0.0001*
ALT (IU/L)	41.65±62.68	129.81±92.88	250.95±182.20	F=41.13 P<0.0001*
SAP (U/L)	81.99±159.93	469.58±175.15	502.44±195.42	F=95.48 P<0.0001*
LDH	104.54±57.89	258.45±59.48	267.25±62.48	F=124.0 P<0.0001*
Bile acid level (mol/L)	21.97±5.01	59.87±8.94	142.71±9.87	F=215.84 P<0.0001*

Table no.3 shows that the serum bilirubin was significantly higher in women with severe cholestasis [0.71±0.25], followed by moderate cholestasis [0.61±0.24] and mild cholestasis [0.59±0.21]. The AST was also higher in women with severe cholestasis [228.05±151.23], followed by moderate cholestasis [116.81±82.10] and mild cholestasis [42.35±49.64], and so on. As the severity of cholestasis increased, the level of liver enzymes also increased. Mean bile acid level in mild cholestasis was 21.97±5.01, in moderate cholestasis was 59.87±8.94 and in severe cholestasis was 142.71±9.87. Statistically, a significant difference was observed in all the liver enzymes and bile acid levels (p<0.0001*) of enrolled women among groups.

Table 4: Vitamin D Status Of Pregnant Women Enrolled In Case And Control Groups

Vitamin D status (ng/ml)	Total	Case [N=70]		Control [N=70]		P- Value
		No.	%	No.	%	
Deficiency (≤10 ng/ml)	30	18	25.71%	12	17.14%	χ^2=6.815
Insufficiency (11-20 ng/ml)	74	41	58.57%	33	47.14%	p=0.0331
Normal (>20 ng/ml)	36	11	15.71%	25	35.71%	
MEAN±SD [RANGE] (ng/ml)		18.75±11.25 [4.00-58.60]		23.65±11.52 [4.00-61.90]		t=2.546 p=0.012

Table 5: Association Of Severity Of Cholestasis And Vitamin D Levels Of Pregnant Women Enrolled In Case And Control Groups

	VITAMIN D LEVEL			ANOVA
	No.	Mean±SD	Median (Range)	
No Cholestasis	70	23.65±11.52	21.77 (14.43-29.84)	F=3.961; p=0.0087
Mild Cholestasis (19-40mol/L)	11	20.89±13.25	17.50 (10.00-28.25)	
Moderate Cholestasis (40-99mol/L)	33	19.54±13.08	14.39 (12.94-20.13)	
Severe Cholestasis (≥100mol/L)	26	16.84±9.41	13.90 (11.88-19.85)	

Table no.4 shows that the low vitamin D level was seen in both cases and control. However, the percentage was higher in cases (59/70,84.28%) as compare to control (45/70, 64.28%) and the difference was statistically significant. Normal levels of vitamin D were seen in 35.70% of the controls as compared to 15.71% of cases. The mean vitamin D levels in the case group was 18.75±11.25 ng/ml and in control was 23.65±11.52 ng/ml and the difference was statistically significant [p=0.012].

Most women with no cholestasis [n=70] had normal vitamin D levels [23.65±11.52]. On the contrary, the women with severe cholestasis [n=26] had lowest vitamin D levels [16.84±9.41]. The more the severity of cholestasis, the less the vitamin D level. Statistically, a non-significant difference was observed in the association of severity of cholestasis and vitamin D in enrolled women among groups [p=0.0087].

DISCUSSION

In present study it is found that the mean vitamin D level was lower in the case group compared to controls, statistically, a significant difference was observed in the vitamin D status of enrolled women. Chen J.[17]et al conducted a study in China on 125 pregnant women with intrahepatic cholestasis and 95 healthy women, findings of study suggested the potential role of vitamin D in the pathogenesis of Intrahepatic cholestasis. A similar study was conducted by Türkmen G et al.,[18] aimed to investigate the association between serum Vit D level and ICP, in which they also found that low levels of Vit D were associated with ICP disease and its severity. Anwar M.M. et al. [19] conducted a cross sectional study of 50 patients aged > 3 months up to 18 years in Egypt and revealed that Deficiency of Vitamin D was evident in chronic cholestasis patients. Canverenler E et al [20] conducted a study to evaluate the relationship between plasma 25-hydroxyvitamin D (25(OH)D) levels in Intrahepatic Cholestasis of Pregnancy (ICP) patients and concluded that ICP patients have significantly lower levels of plasma 25(OH)D when their ALT levels are elevated (> 200 U/l). Similarly Kasapoglu et al.[21] 2013 found that there was association of Low vitamin D levels wıth increased risk for fatty liver disease among non-obese adults. Shemer E A W [22] conducted a study in Sweden and depicted that ICP women had significantly (p = 0.0041) lower levels of 1,25-D3 in serum (76.4 ± 23.1 vs. 112.0 ± 40 ng/L, mean ± SD), unrelated to serum bile acids.

CONCLUSION-

As the severity of cholestasis increased, the level of liver enzymes also increased. Pregnant women with cholestasis had lower Vitamin D levels and that lower levels were inversely correlated with bile acid levels and lead to the severity of the disease.

LIMITATIONS:

1. Seasonal variation and sun exposure were not taken into consideration in the present study, as sun exposure affects Vitamin D levels.
2. Sample size was small.
3. Results were confined to a single tertiary care hospital and can not be generalized to entire population.
4. Pre pregnancy Vitamin D level was not noted which could play a significant role in telling whether ICP was the cause or effect of Vitamin D deficiency.

Funding: No funding sources

Conflict Of Interest: None declared

Ethical Approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. Journal of hepatology. 2000 Dec 1;33(6):1012-21.
2. Girling J, Knight CL, Chappell L, Royal College of Obstetricians and Gynaecologists. Intrahepatic cholestasis of pregnancy: Green-top Guideline No. 43 June 2022. BJOG: An International Journal of Obstetrics & Gynaecology. 2022 Dec;129(13):e95-114.
3. Peelen E, Knippenberg S, Muris AH, Thewissen M, Smolders J, Tervaert JW, Hupperts R, Damoiseaux J. Effects of vitamin D on the peripheral adaptive immune system: a review. Autoimmunity reviews. 2011 Oct 1;10(12):733-43.
4. Tan LK. Obstetric cholestasis: current opinions and management. Annals of the Academy of Medicine, Singapore. 2003 May 1;32(3):294-8.
5. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstetrics &

Gynecology. 1999 Aug 1;94(2):189-93.
6. Woolbright BL, Jaeschke H. Novel insight into mechanisms of cholestatic liver injury. World journal of gastroenterology. 2012 Sep 9;18(36):4985.
7. Kosters A, Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. InSeminars in liver disease 2010 May;30(2):186-194.
8. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World journal of gastroenterology. 2009 May 5;15(17):2049.
9. Hu R, Yin H, Li X. Changing trends of adverse pregnancy outcomes with maternal pre-pregnancy body mass index: a join-point analysis. Frontiers in Medicine. 2022;9.
10. Zollner G, Trauner M. Nuclear receptors as therapeutic targets in cholestatic liver diseases. British journal of pharmacology. 2009 Jan;156(1):7-27.
11. Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. Journal of perinatology. 2006 Sep;26(9):527-32.
12. Germain AM, Carvajal JA, Glasinovic JC, Sumie KC, Williamson C. Intrahepatic cholestasis of pregnancy: an intriguing pregnancy-specific disorder. The Journal of the Society for Gynecologic Investigation: JSGI. 2002 Jan;9(1):10-4.
13. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005 Sep 1;129(3):894-901.
14. Seamans KM, Cashman KD. Existing and potentially novel functional markers of vitamin D status: a systematic review. The American journal of clinical nutrition. 2009 Jun 1;89(6):1997S-2008S.
15. 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.
16. Girling J, Knight L.C, Chappel L.RCOG green-top guideline no.43 June2022. BJOG . August 2022.
17. Chen J, Ding X, Yang K, Yin P. Intrahepatic Cholestasis of Pregnancy Associated Vitamin D deficiency. Forest Chemicals Review. 2021 Aug 31:1511-5
18. Gençosmanoğlu Türkmen G, Vural Yilmaz Z, Dağlar K, Kara Ö, Sanhal CY, Yücel A, et al. Low serum vitamin D level is associated with intrahepatic cholestasis of pregnancy. Journal of Obstetrics and Gynaecology Research. 2018 Sep;44(9):1712-8.
19. Manal M. Anwar1 , Ahmed E. Arafa , Dalia S. Morgan , Khaled K. Mohamed. Association between vitamin D level and patients with cholestasis. International Journal of Community Medicine and Public Health. 2018 May;5(5):1713-1718.
20. Canverenler E, Buke B, Akkaya H, Demir MB, Guven C and Gundem G.Vitamin D Levels in Women with Intrahepatic Cholestasis of Pregnancy. Insights of Biomedical Research. 2017;1(1):1-4.
21. Kasapoglu B, Turkay C, Yalcin KS, Carlioglu A, Sozen M and Koktener A. Low vitamin D levels are associated with increased risk for fatty liver disease among non-obese adults. Clinical Medicine Journal. December 2013. Available at https://www.rcpjournals.org/content/clinmedicine/13/6/576
22. Elisabeth Andrea Wikström Shemer. Decreased 1,25-dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstetricia et Gynecologica Scandinavica. November 2010, 89(11):1420-3.