ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 4, Issue – 6, November – December - 2021, Page No. : 107 – 115

Association of intrahepatic cholestasis in pregnancy with gestational diabetes mellitus and dyslipidemia

[1]Dr Aditi Bansal, Associate Professor, SMS Medical College, Jaipur, Rajasthan,

[2]Dr.Nivesh Lal, Intern, JNU Medical College, Jaipur, Rajasthan,

[3]Dr Richa Gupta, Assistant Professor, SMS Medical College, Jaipur, Rajasthan

[4]Dr. Sapna Choudhary, Resident, SMS Medical College, Jaipur, Rajasthan

[5]Dr Pravesh Kumari, Resident, SMS Medical College, Jaipur, Rajasthan

Corresponding Author: Dr. Sapna Choudhary, Resident, SMS Medical College, Jaipur, Rajasthan

How to citation this article: Dr. Aditi Bansal, Dr. Nivesh Lal, Dr Richa Gupta, Dr. Sapna Choudhary, Dr Pravesh Kumari, "Association of Intrahepatic Cholestasis In Pregnancy With Gestational Diabetes Mellitus And Dyslipidemia", IJMACR- November – December - 2021, Vol – 4, Issue - 6, P. No. 107 – 115.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction: Intrahepatic cholestasis of pregnancy (ICP) is a most common pregnancy-related liver disorder. It frequently develops in late pregnancy. It is associated with increased rates of maternal and foetal adverse outcomes including spontaneous preterm labour, foetal hypoxia, meconium-stained liquor and stillbirth. Liver is a central organ in major metabolic pathways in body namely lipogenesis, gluconeogenesis and cholesterol metabolism. Hence pathological conditions with diseased liver can manifest with deranged metabolic profile including glucose intolerance and dyslipidemia.

Aims and Objectives: This study aims to determine the association between ICP with gestational diabetes mellitus (GDM) and dyslipidemia.

Material &Methods: It was a prospective observational study conducted in the Department of OBG S.M.S. Medical College, Jaipur. Two groups with 30 patients in each group were included in this study. Cases were diagnosed by h/o pruritus at 24 weeks and above and controls were without h/o ICP. Both groups were subjected to DIPSI testing. Both the groups were advised to eat 3 healthy meals a day and following overnight fasting serum lipid profile testing was done by UV enzymatic method, which includes assessment of total cholesterol, LDL cholesterol, serum triglycerides and HDL cholesterol levels. Results were tabulated and statically analysed by using SPSS software.

Results: ICP women were belonging to mean age group of 22.2 ± 1.85 years. Serum bile acid was found to be significantly higher in ICP group (35.97 ± 26.47) compared to control subjects (4.19 ± 0.84 µmol /L) with p <0.001. Mean DIPSI was higher in intra hepatic cholestasis cases (153.4 ± 44.6 mg/dl) as compared to controls (118.2 ± 40.9 mg/dl) and statistically significant (p=0.002). Serum total cholesterol levels were higher in

ICP group (337.3 ± 155.1) as compared with the control subjects (193.4 ± 48.38 mg/dl) and this difference was found to be statistically significant (p <0.001).

Conclusion: ICP is characterized by glucose intolerance and dyslipidaemia, consistent with the changes seen in the metabolic syndrome. GDM also occurs more commonly in pregnancies complicated by ICP. Given the growing evidence in support of an association between ICP and GDM, ICP and dyslipidemia, Further work is required to help clarify which metabolic pathways are altered in ICP in order to better promote both maternal and fetal well-being.

Keywords: Intrahepatic cholestasis, Diabetes mellitus, dyslipidemia, Bilirubin

Introduction

ICP is a common liver disease during pregnancy[1], with reported incidence rates of between 0.4 and 15% in different countries and populations[2]. ICP is characterised by otherwise unexplained pruritus, with elevated bile acids and/or serum transaminases in the late second and third trimester of pregnancy. Pruritus spontaneously resolves and deranged liver function tests typically normalize within 4 weeks of delivery[3].

Liver is a central organ in major metabolic pathways in body namely lipogenesis, gluconeogenesis and cholesterol metabolism. Cholestasis associated changes in glucose and lipid metabolism may potentially be explained by bile acid receptors such as farnesoid X receptor and TGR5 (G-protein coupled bile acid receptor) which are also involved in glucose and lipid metabolism [4,5]. Hence pathological conditions with diseased liver can manifest with deranged metabolic profile including glucose intolerance and dyslipidemia [6,7].

In the pathogenesis of ICP, progesterone metabolites seem to play an important role[8]. In liver progesterone is reduced to pregnenolone and pregnanediol. Four different isomers (3α/3β and 5α/5β) are formed, which are further metabolized by hydroxylation and conjugation with sulfate and glucuronic acid. 3α and 5α isomers of progesterone are substantially increased in patients with ICP. These sulphated metabolites of progesterone have been shown to antagonize farnesoid-X receptor (FXR) and hence affects metabolism of bile, glucose and lipids[9].

The mechanism of changes in glucose metabolism may potentially be related to reduced activity of FXR which influences glucose, lipid and bile acid homeostasis. As mentioned above ICP patients have down regulated FXR function due to antagonism by sulfated progesterone metabolites. Physiologically, primary bile acids- cholic acid and chenodeoxycholic acid, suppress the expression of key enzymes involved in gluconeogenesis by interaction with FXR[10].Additionally bile acids have recently been reported to act synergistically with glucose to promote β-cell insulin secretion[11], as well as induce expression of insulin-regulated glucose transporter GLUT-4 through FXR mediated pathways[12]. Disruption in these homeostatic pathways may promote impaired glucose tolerance observed in ICP.

In pregnancy, with ICP associated with an abnormal lipid profile. Total cholesterol and LDL increase, HDL decrease during pregnancy in women with ICP. Possible mechanism is, FXR stimulate expression of peroxisome proliferator activated receptor-α(PPAR-α), which is a nuclear receptor responsible for regulation of expression of receptor for apolipoprotein A1(a major component of HDL). FXR receptor activity is influenced by progesterone metabolites

The purpose of this study is to investigate the association between ICP with GDM (gestational diabetes mellitus) & dyslipidemia, to know if further monitoring of metabolic

profile in cases of ICP would help us to predict complications, so that timely intervention can result in an improved feto-maternal outcome

Aim and Objective

To determine association between intrahepatic cholestasis of pregnancy (ICP) with gestational diabetes mellitus and dyslipidemia

Material and method

This is prospective observational study, conducted in department of Obstetrics and Gynaecology, S.M.S. Medical College and attached group of hospitals, Jaipur. Cases included in the study were the women diagnosed with intra-hepatic cholestasis of pregnancy. Similar Age, BMI and gestation matched pregnant females without intra-hepatic cholestasis of pregnancy were included in control group.

Sample size is calculated at 80% study power and alpha error of 0.05%, assuming 30% GDM in pregnancy with ICP and 0.01% GDM in pregnancy without ICP[20]. Following above assumption 22 pregnant females with ICP and 22 pregnant females without ICP are required for this study. It is further enhanced and rounded off to 30 patients in each group as the final sample size for present study expecting 30% drop outs / lost to follow up.

Inclusion Criteria

- Women admitted in hospital with singleton pregnancy.
- Age group: 20-25 years.
- Gestational age: 24 weeks to term
- BMI: 18.5 -24.9kg/m²

Exclusion Criteria

- Other causes of hepatic dysfunction
  - Preeclampsia
  - HELLP syndrome
  - Acute fatty liver of pregnancy
  - Primary biliary cirrhosis
  - Active viral hepatitis
  - USG abnormality suggesting any biliary obstruction
- History of previous gestational or pre-conceptional diabetes.
- Use of oral/intramuscular steroids, calcineurin inhibitors, beta blockers.
- Multiple gestation.
- Pregnant women with history of pruritus at 24 weeks and above, and fulfilling the inclusion criteria, were included in case group and subjected to testing of serum bile acids and liver transaminases. ICP was diagnosed if the serum bile acid level is > 10µmol/L and SGOT /SGPT (more than twice the normal) are elevated. Control subjects were matched for BMI (±3.0kg/m²), maternal age (±2 years), gestational age (±2 weeks).
- Both groups were subjected to DIPSI testing with 75 gm oral glucose and results obtained after 2hours.
- Both the groups were advised to eat 3 healthy meals a day and following overnight fasting serum lipid profile testing was done by UV enzymatic method, which includes assessment of total cholesterol, LDL cholesterol, serum triglycerides and HDL cholesterol levels.

Results were collected and statistical analysis was done.

Statistical Analysis

Data collected was entered in MS Excel sheet. Continuous variables were summarized as Mean and Standard Deviation, whereas nominal / categorical variables as percentage and proportions. Unpaired t test was used for analysis of continuous variables whereas chi square test / Fischer exact test was be used for categorical or nominal variables. P value < 0.05 was taken as

significant. MEDCALC 16.4 version statistical software was used for all statistical calculations.

Results

Table 1: Demographic features, Clinical features and Lab Investigations

	Case	Control	P- Value
AGE (Mean +/- SD)	22.2 ± 1.85	22.83 ± 1.76	p = 0.179
BMI (Mean +/- SD)	22.98 ± 1.36	23.25 ± 0.96	p = 0.371
Gestational age (%)			p = 0.684
<34 weeks	16.7	13.3	
34 – 37 weeks	60	53.3	
>37 weeks	23.3	33.3	
Clinical features			
Pruritus (%)	100		
Icterus (%)	16.7		
Lab Investigations			
Total Bilirubin	0.8 ± 0.4	0.8 ± 0.5	0.645
Direct Bilirubin	0.3 ± 0.2	0.3 ± 0.2	0.248
Indirect Bilirubin	0.5 ± 0.2	0.5 ± 0.3	0.964
SGOT (U/L)	77.2 ± 70.1	70 ± 81.5	0.718
SGPT (U/L)	113 ± 128.5	85.8 ± 100.3	0.366
Bile Acid Level (µmol/L) (Mean +/- SD)	35.97 ± 26.47	4.19 ± 0.84	P < 0.001

Table 2: Comparison of DIPSI values (mg/dL) among study groups

Group	N	Mean ± SD	Median (Range)
Case	30	153.4 ± 44.6	154 (87 – 274)
Control	30	118.2 ± 40.9	110 (47 – 242)
t test = 3.289 with 58 degrees of freedom; p = 0.002 (S)			

Table 3: Distribution of study subjects according DIPSI values

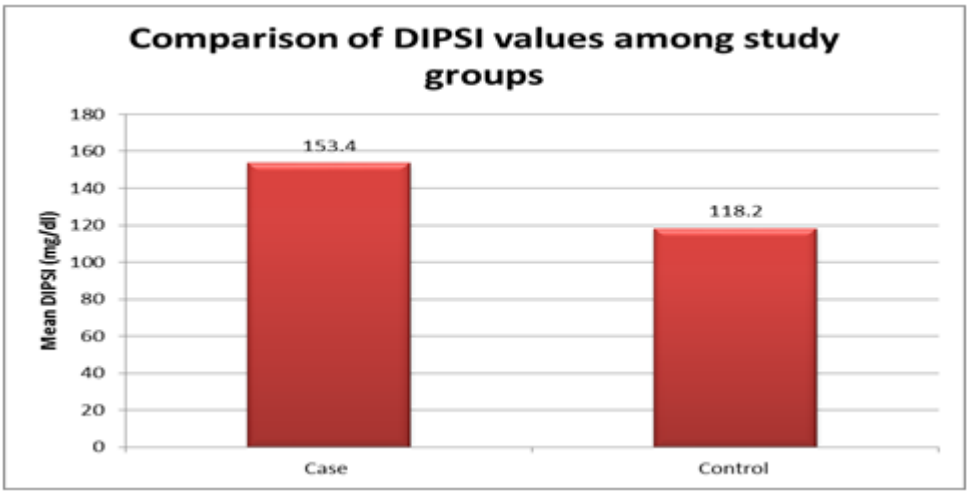
DIPSI	Case		Control		Total	
	N	%	N	%	N	%
≥140 mg/dL	22	73.3	8	26.7	30	50
<140 mg/dL	8	26.7	22	73.3	30	50
Total	30	100	30	100	60	100

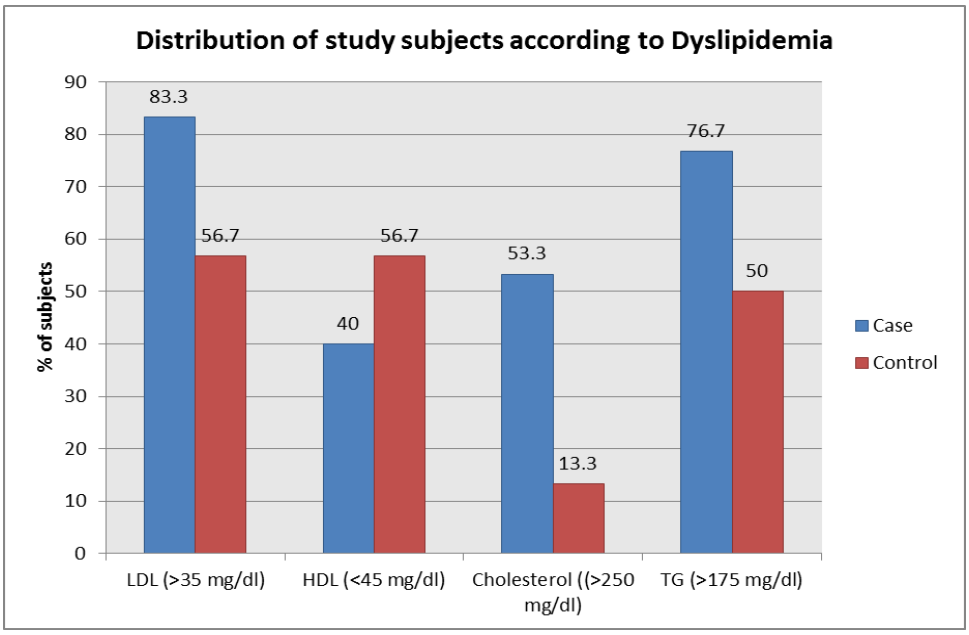
Table 4: Comparison of lipid profile among study groups

Lipid profile	Cases	Controls	P value
Total cholesterol (mg/dl)	337.3 ± 155.1	193.4 ± 48.38	<0.001 (S)
HDL (mg/dl)	51.88 ± 17.9	47.61 ± 13.76	0.305
LDL (mg/dl)	51.15 ± 14.76	43.94 ± 22.13	0.143
TG (mg/dl)	236.7 ± 74.78	199.9 ± 81.37	0.073

Table 5: Distribution of study subjects according to dyslipidemia

Abnormal Lipid profile	Case		Control		P value
	N	%	N	%	
LDL (>35 mg/dL)	25	83.3	17	56.7	0.047 (S)
HDL (<45 mg/dL)	12	40	17	56.7	0.301
Cholesterol (>250 mg/dL)	16	53.3	4	13.3	0.002 (S)
TG (>175 mg/dL)	23	76.7	15	50	0.060





Discussion

We investigated the association of intrahepatic cholestasis of pregnancy with gestational diabetes mellitus and dyslipidemia. Both the groups (case/control) were matched in the socio- demographic profile. The mean age of intra hepatic cholestasis cases was 22.2 ± 1.85 years, while that of control group was 22.83 ± 1.76 years with no significant difference was seen (p=0.179). This could be because of early age at first child birth in Indian population. Mean BMI of intra hepatic cholestasis cases was 22.98 ± 1.36 Kg/m^2 (19.6 – 24.8 Kg/m$^{2)}$, while among controls the mean BMI was 23.25 ± 0.96 Kg/m^2 (20.7 – 24.6 Kg/m^2) (p=0.371). In a study done by Antony T. Dann et al (2006)[15], in the intrahepatic cholestasis of pregnancy group, the median gestation at diagnosis being 33 + 4 weeks (range 12 + 0 to 40 + 5) weeks and the onset of pruritus occurred at 30 (range 4–39) weeks, as recalled by women at the time of recruitment. These findings were consistent with our study.

Pruritus was found in all cases with intrahepatic cholestasis while icterus was found only in 16.7% these cases. The liver enzymes were slightly higher in intra hepatic cholestasis cases as compared to controls, but this difference was not found to be statistically significant (p>0.05), as seen in table 1. The liver transaminases were raised in cases (SGOT was twice the normal in 70% cases & SGPT was twice the normal in 73.3% cases), while among controls none of the subjects had SGOT or SGPT raised to twice the normal value. This difference in SGOT and SGPT level between the two groups was found to be statistically significant (p value <0.001). However, no significant difference with respect to serum bilirubin level was found between case and control groups. The serum bile acids were found to be significantly higher in ICP group (35.97 ± 26.47) compared to control subjects (4.19 ± 0.84 µmol /L) with p <0.001. These results were consistent with the study done by Martineau et al (2014)[14.]

The mean DIPSI values were higher in intra hepatic cholestasis cases (153.4 ± 44.6 mg/dL) as compared to controls (118.2 ± 40.9 mg/dL), this difference was found to be statistically significant (p=0.002)as shown in table 2. Results were similar to the observations obtained by

Marcus et al (2015)[13] (metabolic profile in ICP) as maternal blood glucose concentrations were significantly increased in ICP using ambulatory CGM (P < 0.005) and following a GTT (P < 0.005) in their study. Similarly, a study conducted by Gulenay Gencosmanoglu Turkmen et al (2019)[16] was also consistent with our study. They observed that the mean 50-gm GCT values were significantly higher in the pregnant women with ICP compared to the healthy controls (128.7±28.2, 106.6±27.0; p <0.0001) and it was slightly higher in women with severe disease than women with mild disease (132.7±30.1, 125.5±26.5; p=0.26).

In our study, we observed that the DIPSI values (single step with 75 gm glucose using >/=140 mg/dL as cut-off) was positive in 73.3 % of the cases whereas, only 26.7% of the controls were found to have positive DIPSI values (table3). Similar study done by Martineau, Christina Raker et al (2014)[14] showed that compared to the control group the incidence of GDM in pregnancies complicated by ICP was 13.6% (OR 1.68 CI1.04–2.72, p = 0.03). When the ICP group was divided into women in whom GDM screening was performed before and after a diagnosis of ICP, the incidence of GDM was found to be 13.4% in the cases screened before they developed ICP (OR 1.66 CI 0.89–3.10, p = 0.11), rising to30% (OR 4.69 CI 1.98–11.1, p = 0.0002) following the onset of cholestasis . The statistically significant association between ICP and GDM in the group as a whole remained after adjustment for racial group, a variable known to influence the risk of both ICP and GDM, (unadjusted OR 1.68 95% CI 1.04–2.72, p = 0.03 vs. adjusted OR 1.69 95% CI 1.04–2.75, p = 0.03).

Serum total cholesterol levels were higher in the ICP group (337.3± 155.1) as compared with the control subjects (193.4 ± 48.38 mg/dl) and this difference was found to be statistically significant (p <0.001). The mean HDL, LDL and TG levels were not significantly different among the two groups as seen in table 4.

Serum LDL levels were raised in 83.3% cases as compared to 56.7% of controls and this difference was found to be statistically significant (p value = 0.047). Similarly serum cholesterol levels were also raised in 53.3% cases as compared to 13.3% of controls and this difference was found to be statistically significant (p = 0.002) as seen in table 5. All these findings indicate significant association between intra hepatic cholestasis of pregnancy and dyslipidemia. These observations were consistent with the observations made by Dann et al. (2006) that assessed plasma lipid concentrations in non-fasting blood samples from 132 pregnant women (63 women with ICP) during pregnancy and at 4-6 weeks postpartum. In the ICP group, Triglyceride concentrations were significantly elevated compared to controls either during the gestational or postnatal period (p = 0.001). These observations were also consistent with the observations studied by Marcus et al (2015) (metabolic profile in ICP) as lipid profiles of women with ICP showed significantly higher fasting total cholesterol and LDL cholesterol levels compared with the control groups. In addition, HDL cholesterol was significantly reduced, with a corresponding increase in the total cholesterol/HDL ratio in ICP as per their study. However, in our present study although mean HDL and triglycerides levels were not different and statistically significant in the two groups but it was found that there was a higher percentage of increased triglyceride levels (>175 mg/dL) in the cases (76.7%) as compared with the control groups (50%). Similarly, a study conducted by Jin et al (2016), suggested that hypertriglyceridemia could be considered as significant predictor of ICP. High

triglyceride levels at second trimester were significantly associated with an increase in the morbidity of ICP (p=0.006, AOR=1.50, 95% CI:1. 12-2.00). These results were consistent with our study.

Conclusion

ICP is a pregnancy specific disorder which typically commences in the late second or third trimester and resolve after delivery. It is characterized by mild to severe pruritus, without any specific dermatologic features, elevated liver enzymes and increased serum bile acids. The etiology of ICP is still not completely explicit. Pathogenesis includes a combination of hormonal and environmental factors superimposing on a genetic predisposition. During recent years ICP is recognized to be associated with an abnormal metabolic profile, including glucose intolerance and dyslipidemia although it is considered to be secondary to aberrant bile acid homeostasis. Total serum bile acids typically peak 30–90 minutes after meals. The criteria for diagnosing ICP are subjective & there are no current uniform criteria for the diagnosis of ICP. Most studies use elevated serum bile acids or serum transaminase levels combined with pruritus during pregnancy; however, the serum bile acids may not necessarily be elevated at the time of a blood drawn due to fasting versus non fasting state and there may be a greater rise towards the later weeks of pregnancy. The turnaround time for receiving the laboratory results may be 1–2 weeks, making it an impractical tool for immediate risk stratification. In present study, gestational diabetes mellitus and dyslipidemia were found to be associated with ICP. Hence, DIPSI values and lipid profile should be estimated in ICP women. Large scale clinical trials are required to discover which metabolic pathways are altered in ICP.

In our study sample size was small. For more conclusive evidence, larger number of cases needs to be studied. The study was done at Tertiary Care Hospital; thus, it is not representative of the whole population. More multi-centric trials need to be done.

References

1. Joshi D, James A Quanglia A, west brook RH, Heneghan MA, liver disease in pregnancy. Lancet 2010;375 : 594-605.
2. Geenes V, Williamson C, intrahepatic cholestasis of pregnancy. Word J Gastroenterol 2009; 15:2049-66.
3. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014;124:120-133.
4. Pineda Torra I, Claudel T, Duval C, Kosykh V, Fruchart JC, Staels B. Bile acids induce the expression of the human peroxisome proliferator activated receptor alpha gene via activation of the farnesoid X receptor. Mol Endocrinol 2003;17:259–272.
5. Cariou B, Staels B. FXR: a promising target for the metabolic syndrome? Trends Pharmacol Sci 2007;28:236–243.
6. Fiorucci S, Mencarelli A, Palladino G, Cipriani S. Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. Trends Pharmacol Sci 2009;30:570–580.
7. Sharma R, Long A, Gilmer JF. Advances in bile acid medicinal chemistry. Curr Med Chem 2011;18:4029–4052.
8. S Jovall J, Reyes H. Bile acids & progesterone metabolites in intrahepatic cholestasis of pregnancy. Ann Med 2000; 32:94-106.
9. Abu-Hayyeh S, Papacleovoulou G, Lovgren-Sandblom A, et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone

metabolites inhibit farnesoid X receptor resulting in a pro-cholestatic phenotype. Hepatology 2013;57:716–72.

10. Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006;116:1102–1109.
11. Shen H, Zhang Y, Ding H, et al. Farnesoid X receptor induces GLUT4 expression through FXR response element in the GLUT4 promoter. Cell Physiol Biochem 2008; 22: 1-14.
12. Roberts RE, Glicksman C, Alaghband-Zadeh J, et al. The relationship between postprandial bile acid concentration, GLP-1, PYY and ghrelin. Clin Endocrinol 2011; 74: 67-72.
13. Marcus G Martineau et al. (2015) Metabolic profile of Intrahepatic cholestasis of pregnancy is associated with impaired glucose tolerance, dyslipidemia & increased fetal growth: Diabetes Care 2015; 38; 243-248/ Doi:10.2337/dc14-2143.
14. Marcus Martineau, Christina Raker, Raymond Powrie, Catherine Williamson Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes. European Journal of Obstetrics & Gynecology and Reproductive Biology 176 (2014) 80–85.
15. Anthony T. Dann, Plasma Lipid Profiles of Women With Intrahepatic Cholestasis of Pregnancy (Obstet Gynecol 2006; 107:106–14).
16. Gulenay Gencosmanoglu Turkmen. Intrahepatic cholestasis of pregnancy is associated with Gestational Diabetes Mellitus Gynecol Obstet Reprod Med 2019; 25(0):000-000.