

Risk Factors Associated with Cholelithiasis during Pregnancy and Postpartum

Shaimaa Belal¹, Hesham Mohammed Hamed², Abdelrahman Kamal³,
Manal Abdel-Wanees Al-Sayed^{2*}, Hany Mahmoud Abd El Hamid²

¹Department of Obstetrics and Gynecology, Faculty of Medicine, Helwan University, Helwan, Egypt

²Department of Obstetrics and Gynecology, El-Sahel Teaching Hospital, Cairo, Egypt

³Department of General Surgery Sahel Teaching Hospital, Cairo, Egypt

Email: *amrh1933@gmail.com

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Abstract

Gallbladder disease is the most common non-obstetrical cause of maternal hospitalization in the first year postpartum. Many risk factors have been associated with gallbladder disease in pregnancy including body mass index, prenatal weight gain, prenatal physical activity, dietary fat, age, parity, a history of gallbladder disease and the number of previous pregnancies were significant factors related to new gallstones and biliary sludge formation in the pregnant group. The aim of this study is to evaluate the risk factors for gallstones formation in pregnancy and one year after labour. The study included 328 female patients (pregnant or postpartum) divided into two groups; patient group (164 patient) that are pregnant or postpartum patient have gallstones and control group (164 patient) that are pregnant or postpartum patient does not have gallstones. All patients were subjected to full history taking; especially about risk factors predisposing for gallstones, physical examination and pre-operative routine laboratory investigations and imaging as abdominal ultrasound study (U/S). Obesity, young age, history of gallbladder disease and use of estrogen and progesterone are the main risk factors that increase incidence of gallstones during pregnancy or one year postpartum. Use of vit C, iron, drinking coffee and practicing regular physical activity are considered protective factors.

Keywords

Cholelithiasis, Pregnancy, Postpartum

1. Introduction

Gall stones are the most common biliary pathology, 10% to 15% of adult popula-

tion in the American united states had gallstones, while as high as 60% of Indians over 35 years of age and as low as in Japanese women 3.2%. No accurate record of the incidence or prevalence of gall stones in Arab countries. For a long time this disease was known to be of fatty fertile fifty female, these facts need to be reviewed. There has been a significant increase in the incidence of gallstones in patients less than 30s of age in the past 10 years also there is a change toward asthenic female [1].

The incidence of gallstones disease ranges from 3.3% to 12% in pregnant women. Gallbladder disease is the most common non-obstetrical cause of maternal hospitalization in the first year postpartum [2]. High levels of estrogen and progesterone were considered to be the main cause of sludge during pregnancy; not only pregnancy itself but also dehydration, prolonged fasting, and acute weight loss could be the main causes for sludge only during hyperemesis gravidarum [3]. Pregnancy is a major risk factor for the development of cholesterol gallstones. Cholesterol gallstones result from a biochemical imbalance of lipids and bile salts in the gallbladder bile [4].

The risk for cholesterol gallstones rises incrementally by 8% with each additional birth. We also found that after accounting for the number of children, 12 months of breast feeding reduces the risk of gallbladder disease in parous women by 7% [5].

Many risk factors have been associated with gallbladder disease in pregnancy including body mass index, prenatal weight gain, prenatal physical activity, dietary fat, age, parity, a history of gallbladder disease and the number of previous pregnancies were significant factors related to new gallstones and biliary sludge formation in the pregnant group [6]. Epidemiological studies revealed decreased risk of cholecystectomy with coffee, nut, recreational physical activity, vitamin C supplementation [7]. Dietary factors that may prevent the development of gallstones include polyunsaturated fat (as Sunflower Seeds and Olive Oil), monounsaturated fat (as nuts), fiber and caffeine. Consuming vegetarian diet is also associated with decreased risk. Nutritional supplement that may help prevent gallstones include vitamin C, soy lecithin, iron [8].

2. Aim of the Work

The aim of this study is to evaluate the risk factors for gallstones formation in pregnancy and one year after labour.

3. Patients and Methods

This study was carried out the period from October 2020 to October 2021 at El-Sahel teaching hospital.

Patients: The study included 164 female patients with gallstones, 48 cases of them were pregnant and 116 cases of them were within the first year post-partum.

Controls: The study included 164 female patients as a control without gallstones; 50 cases of them were pregnant and 114 cases of them were within the

first year post-partum.

Inclusion criteria: females in fertility period (pregnant or menstruating).

Exclusion criteria: pre-pubertal or post-menopausal females.

1) Pre-operative evaluation:

A. Detailed history. B. General and local examination.

C. Evaluation of risk factors for gallstone formation in patients and control group.

a) *Risk factors that increase gallstones formation*

- Genetics: we ask for family history of gallstones especially in first degree relatives.
- Age.
- Number of pregnancies: we ask for number of previous pregnancies.
- Hyperemesis gravidarum: we ask for history of hyperemesis gravidarum during first trimester.
- Diabetes mellitus: we ask if the patient is diabetic.
- Hepatitis: we ask if the patient suffers from hepatitis B or C.
- Estrogen or progesterone supplementation: we ask if the patient takes any hormonal supplementation during pregnancy or postpartum.
- Fat diet: we ask for ingestion of fatty diet.
- Body mass index: $BMI = kg/m^2$.

b) *Protective factors that decrease gallstones formation*

- Breast feeding: we ask about artificial or breast feeding.
- Physical activity: we ask if the patient was practicing any type of physical activity.
- Coffee: we ask about daily intake of coffee.
- Vegetable: we ask about ingestion of vegetable diets.
- Iron: we ask about history of iron supplementation during pregnancy or postpartum.
- Vitamin C: we ask about vitamin C supplementation during pregnancy or postpartum.
- Statin: we ask for intake of statins for hypercholesterolemia.
- Ursofalk: we ask for intake of ursofalk for any gallbladder or liver disease.
- Eztabie: we ask for intake of eztabie for hypercholesterolemia.
- D. Pre-operative investigations for patients:

a) *Routine preoperative Laboratory investigations.*

b) *Abdominal ultrasonography:* With stress on gallbladder (size, wall thickness, stones, signs of acute inflammation), common bile duct and intrahepatic biliary radicles.

2) Operative techniques for patients: all patients were operated upon in the postpartum period either by open or laparoscopic technique. Pregnant females were managed conservatively then operated upon after labour (40 of them underwent laparoscopic cholecystectomy and 2 underwent open cholecystectomy) and 116 coming after labour were operated upon (92 underwent laparoscopic

cholecystectomy and 24 underwent open cholecystectomy).

3) Post-operative care:

- Monitoring of the vital signs of the patients every one hour, and the amount of the drain every 12 hours.
- Patients were encouraged for early mobilization from bed after 6 hours and started oral intake on regaining of intestinal motility.
- Post-operative analgesia was given as intramuscular diclofenac sodium 75 mg.
- Follow up of any post-operative complications.
- The drain was removed when the serous discharge decreased to less than 30 ml in 24 hours.
- The sutures of the wound were removed from days 10 - 12.

Post-operatively all patients were submitted to careful follow up by:

Data were coded, entered and analyzed using EPI-INFO and SPSS version 19.

4. Results

The patients ages in our study ranged from 20 - 44 years with mean age of 29 years for cases and 27 years for control as shown in **Table 1**. From those 164 cases, 48 patients (29.2%) were pregnant, and 116 patients (70.7%) were post-partum, as shown in **Table 2**. The prevalence of overweight and obesity (Body mass index "BMI" > 25 kg/m²) was higher in patients than in controls (75.6% in patients vs. 53.7% in controls) with significant difference (P = 0.003). The incidence of use of estrogen and/or progesterone in the form of oral contraceptive pills after labour or hormonal support in early pregnancy was significantly higher in patients than control (56.1% in patients vs. 26.8% in controls) with highly

Table 1. Shows the age distribution.

Age groups/year	Cases		Control	
	No	Percentage	No	Percentage
20 - 25	56	34%	62	37.8%
26 - 30	48	29.2%	64	39%
31 - 35	20	12.1%	30	18.2%
36 - 40	36	21.9%	8	0.048%
41 - 44	4	0.024%	0	0%
Total	164	100%	164	100%

Table 2. Shows prenatal and postnatal state.

	NO of cases (%)	NO of control (%)
Pregnant	48 (29.2%)	50 (30.4%)
Postpartum	116 (70.7%)	114 (69.5%)
Total	164 (100%)	164 (100%)

significant difference ($P \leq 0.001$). Also familial history of gallbladder disease is significantly higher in patients than control (12.2% in patients vs. 0% in controls) ($P = 0.001$) and the incidence of gallstones in pregnant or postpartum at young age (<33 year) is high in cases than control (84.1% in patients vs. 68% in controls) ($P = 0.017$). Obesity, young age, history of gallbladder disease and use of estrogen and progesterone are the main risk factors that increase incidence of gallstones formation during pregnancy or one year postpartum (**Table 3**).

The incidence of use of vitamin C was lower in patients than in controls (17.1% in patients vs. 36.6% in controls) ($P = 0.005$) and the prevalence of physical activity practice was lower in patients than in controls (7.3% in patients vs. 22.0% in controls) ($P = 0.008$). But the incidence of use of iron was significantly lower in patients than in controls (75.6% in patients vs. 95.1% in controls) ($P < 0.001$) and the prevalence of drinking coffee was significantly lower in patients than in controls (4.9% in patients vs. 36.6% in controls) ($P < 0.001$) (**Table 4**). According to our study 70.8% of cases were presented postpartum and 29.2% of cases were presented during pregnancy (**Table 5**). According to our study 80.5%

Table 3. Distribution of risk factors that increase frequency of gall bladder stones formation among cases and control.

	Cases N= 164 (N & %)	Control N= 164 (N & %)	Odds ratio (95% CI)	χ^2	P
<i>Age (years) <33</i>	138 (84.1)	112 (68.3)	2.46 (1.09 - 5.61)	5.69	0.017
<i>Age (years) ≥33</i>	26 (15.9)	52 (31.7)			
<i>Family history of GS</i>	28 (17.1)	20 (12.2)	1.48 (0.57 - 3.89)	0.78	0.377
Hepatitis B, C	4 (2.4)	0 (0.0)			0.496
DM	8 (4.9)	0 (0.0)			0.12
History of GB disease	20 (12.2)	0 (0.0)		10.65	0.001
<i>Est/prog use</i>	92 (56.1)	44 (26.8)	3.48 (1.72 - 7.09)	14.47	<0.001
<i>Hyperemesis gravidarum</i>	56 (34.1)	52 (31.7)	1.12 (0.55 - 2.26)	0.11	0.739
<i>No. of pregnancy <3</i>	84 (51.2)	62 (37.8)	1.73 (0.89)	2.99	0.084

Table 4. Distribution of protective factors that decrease frequency of gall bladder stones among cases and control.

	Cases N = 164 (N & %)	Control N = 164 (N & %)	Odds ratio (95% CI)	χ^2	P
<i>Ursosalk</i>	16 (9.8)	0 (0.0)			0.007
<i>Statin</i>	4 (2.4)	0 (0.0)			0.496
<i>Vitamin C</i>	14 (17.1)	60 (36.6)	0.36 (0.16 - 0.78)	7.95	0.005
<i>Iron</i>	124 (75.6)	156 (95.1)	0.16 (0.04 - 0.53)	12.5	<0.001
<i>Breast feeding</i>	132 (80.5)	144 (87.8)	0.57 (0.22 - 1.45)	1.65	0.199
<i>physical activities</i>	12 (7.3)	36 (22.0)	0.28 (0.09 - 0.81)	7.03	0.008
<i>Coffee</i>	8 (4.9)	60 (36.6)	0.09 (0.02 - 0.29)	25.08	<0.001
<i>Vegetable diet</i>	48 (29.3)	52 (31.7)	0.89 (0.43 - 1.83)	0.12	0.734

DM = diabetes Mellitus, est = estrogen, prog = progesteron, BMI = body mass index.

cases were operated laproscopically and 19.5% of cases were operated by open cholecystectomy (**Table 6**). Obesity, young age, history of gallbladder disease and use of estrogen and progesterone are the main risk factors that increase incidence of gallstones during pregnancy or one year postpartum. Use of vitamin C, iron, drinking coffee and practicing regular physical activity are considered protective factors (**Table 7**).

5. Discussion

In this study, we evaluated the risk factors of gallstones formation during pregnancy and one year postpartum. Logistic regression analysis for the most predictor variables of gall stones formation in pregnancy and one-year post-labor among studied cases showed that having a history of gall bladder disease before

Table 5. Onset of presentation of cases of gall bladder stones.

Presentations	No.	%
Onset of compliant during pregnancy		
• 1st trimester	12	7.3
• 2nd trimester	24	14.6
• 3rd trimester	12	7.3
• post labour	116	70.8
Total	164	(100.0)

Table 6. Surgical treatment of cases.

Surgical treatment of cases	No.	%
• open	32	19.5
• Laparoscopy	132	80.5
Total	164	(100.0)

Table 7. Logistic regression analysis for the most predictor variables of gall stones formation in pregnancy and one year post-labour among studied cases.

Predictor variable	B	Wald	Sig.
Age <33 years	1.054	3.357	0.067
BMI >25	1.002	4.034	0.045
GB disease	18.207	2565.9	<0.001
Estrogen/progesterone	1.306.	7.115	0.008
Decreased Vit C	1.485	5.837	0.016
Decreased Iron	1.292	1.768	0.184
Decreased physical activities	1.013	1.186	0.276
Coffee	3.221	8.332	0.004

B = beta co-efficient, Wald = Wald test.

pregnancy is the strongest predictor for cholelithiasis occurrence in this study.

According to this logistic regression analysis there are many other predictors of gallstone formation like overweight, use of estrogen, progesterone as hormonal support in early pregnancy or as oral contraceptive pills in postpartum period, low consumption of vitamin C and coffee. Percentage of cases is more than control in young age <33 year (84.1% vs. 68.3%) while this percentage is less in old ages. P value was 0.017 and this is significant and indicates that early pregnancy predisposes to gallstones than late pregnancy. This does not match with the study done by Tahereh and his co-workers in 2013 that found a positive correlation between mother's age and the risk of sludge/stone formation, but in the study done by KO and his colleagues in 2015 that shows no correlation between mother's age and the risk of sludge/stone formation [9] [10].

In our study, use of estrogen and progesterone (as hormonal support in early pregnancy or as OCP in postpartum period) was a good predisposing factor to gallstone formation as the percentage of cases with gallstone is higher than control (56% vs. 26%) and p value is <0.001. This indicates that use of estrogen and/or progesterone is a risk factor that predisposes to gallstone formation during pregnancy and one year postpartum. These results do not match with that done by KO and his colleagues in 2015 as we evaluated small number of cases [10].

Obesity is a major risk factor for gallstone disease with a linear association between BMI and gallstones incidence this similar to study done by KO and his colleagues in 2015, but this does not match with the study done by Tahereh and his co-workers in 2013. Indeed, BMI was significantly higher in patients with gallstone disease than in controls (75.6% in patients vs. 53.7% in controls) (P = 0.003) [9] [10].

We found no significant difference between patients with gallstones and controls concerning the mean number of pregnancies as that reported in the study done by Simona and his co-workers 2018, despite the data from literature suggesting the importance of the pregnancy number as a lithogenic risk [11].

In our study, cholelithiasis occurrence was not found to have a significant relationship to the dietary fat intakes of the pregnant women. The percentage of fatty diet user was not significantly higher in cases than controls (65% vs. 56%). On the other hand, increased dietary fat intake seemed to provide a protective function for cholelithiasis occurrence [12].

In another study, the higher fat diets resulted in maximal gallbladder emptying, and yet there was substantial stone formation [13].

Family history of gallstone is not significantly higher in cases than controls (17% vs. 12%). This result is like that done by Tahereh *et al.*, 2013 [9].

In the present study, diabetes is not a significant risk factor for gallstone formation (4.9% for cases vs. 0% for controls), but these results don't match with that done by Gunn and his colleagues in 2014, Also in the study done by Simona and his colleagues in 2018 found a higher basal glycaemia and a higher prevalence of diabetes mellitus in patients with gallstone disease than in con-

trols [11] [14].

Prevalence of hepatitis (B, C) in cases is not significantly higher than control (2.4% vs. 0%). This agrees with results found by Tahereh and his colleges in 2013 that found no significant correlation between HBS-Ag positivity and the incidence of biliary sludge/stones [9].

Cholelithiasis occurrences were lower when the pregnant women had consumed dietary iron supplements. No of cases consuming iron was significantly lower than controls (95% vs. 75.6%). This coincides with what's reported by Hamid *et al.*, 2009 [15].

In this study, there was significant relationship between ascorbic acid intake and low incidence of cholelithiasis occurrence. Prevalence of cases is significantly lower in cases than controls (17.1% vs. 36.6%), but in the study done by Glenda and Marilyn, 2014 showed no significant relationship [16].

We found decreased cholelithiasis with daily coffee intake.

Prevalence of cases is significantly lower in cases than controls (4.9% vs. 36.6%). This likes what KO and his colleges in 2015 [10].

Prenatal physical activity was significantly lower in women with cholelithiasis in their pregnancies than in those without cholelithiasis.

Prevalence of cases is significantly lower in cases than controls (7.3% vs. 22%). This coincides with what's reported by Glenda and Marilyn, 2014 [16].

Breast feeding was not significantly lower in cases in comparison with controls. Prevalence of cases is significantly lower in cases than controls (80.5% vs. 87.8%), but this not matches with that found by Bette and his co-workers in 2019 who found that 12 months of breastfeeding reduces the risk of gallbladder disease in parous women by 7% [17].

According to our study consuming two cups of coffee, iron, vit C and ursofalk and practicing daily physical activity are protective factors from cholelithiasis during pregnancy, but intake of eztramibie, statin, vegetable diet and 12 m breast feeding have a role in decreasing incidence for cholelithiasis but its role is not significant.

We recommend repeating this research in different localities and on different number of patients over larger scale to get better results.

6. Conclusions

From this study, we conclude the risk factors that significantly increase the risk for gallstone formation during pregnancy and one year after labor, which are:

*Use of estrogen and or progesterone. *History of gallbladder disease.

*High body mass index. *Early pregnancy (<33 y).

Also, we conclude the protective factors that significantly decrease the risk for gallstone formation during pregnancy and one year after labor which are:

*Iron supplementation. *Drinking daily two cups of coffee.

*Daily practicing physical activity. *Vitamin C supplementation. *Intake of ursofalk.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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