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Epidemiology of Gallstone Disease among Pregnant women in Egypt: Multicenter Study

Saad Motawea[1], Hatem Shalaby[2], Ashraf Ghanem[3] and Ghada El-Khawaga[1*]

[1]Department of Community Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
[2]Obstetrics and Gynecology Department, Obstetrics and Gynecology Hospital, Ain Shams University, Cairo, Egypt.
[3]Obstetrics and Gynecology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Authors SM, HS and AG designed the study, wrote the protocol. Authors GEK and AG managed the literature searches, statistical analysis and wrote the manuscript draft. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: The frequency of gallstone disease among pregnant women attending for antenatal care in Egypt progressively increased during the last few decades. This study aimed to investigate the possible risk factors of gallstone disease among pregnant women attending two obstetrics and gynecology centers in Egypt (Ain Shams Obstetrics and Gynecology University Hospital, Cairo, Egypt and Obstetrics and Gynecology department at Mansoura University Hospital).
Methods: A Case control study was conducted, cases were (170) pregnant women with diagnosed gallstone disease and controls were age matched pregnant women without gallbladder disease (170). Both cases and controls were subjected to interview questionnaire. Nutrient intakes were calculated. Body mass index (BMI) was calculated. Ultrasound examination was performed. Blood samples were analyzed for lipid profile.
Results: Socio-demographic risk factors were illiteracy (OR=14.3), insufficient income (OR=10.6), non working (OR=3) and low social score (OR=3). Reproductive risk factors were previous hormonal contraception (OR=7.9), family history of gall stones (OR=4.2) and parity ≥4 (OR=3.8).

**Corresponding author: Email: ghadaelkhawaga@yahoo.com;*

The risk of gall bladder stone disease increased by increase in BMI (OR=12.8 for BMI ≥ 30 kg/ m^2). The highest risky nutritional behaviors respectively were; the preference of fried meals (OR=41.3), taking more than two food servings rich in animal fat per day (OR=38.9), the habit of eating eastern sweets ≥twice weekly (OR=18.7), food intake between meals (OR=14) and night eating (OR=8.7). The highest risky physical activity score was light physical activity (OR=4.1).
Conclusion: Multiple risk factors were found among pregnant women with gallbladder disease. Most of them are modifiable.

Keywords: Gallstone disease; pregnant; risk factors.

1. BACKGROUND

Biliary calculi were found in an intact gall bladder 1500 BC in ancient Egypt [1]. In western countries, the prevalence of gallstones during pregnancy was reported to be 11% and gallbladder diseases are the second most common indication for nonobstetric surgical intervention in pregnancy [2]. In Egypt, no recent data is available regarding the incidence, prevalence and risk factors of gallstones during pregnancy.

Many risk factors have been associated with gallstone disease, probably some of the most important are obesity, family history of gallstone disease and oral contraceptive use. Other factors like pregnancy or parity are contradictory [2-8].

Diet and sedentary life has long been suspected as modifiable risk factors for gallstone disease, primarily because of indirect evidence from ecological studies and because of their link with obesity [9-11]. Serum lipids and glucose levels are associated with gallstone disease [12-13].

The study aimed to was to investigate the possible risk factors of gallstone disease among pregnant women in Egypt.

2. SUBJECTS AND METHODS

2.1 Study

Case control study.

2.2 Sample

Using Epi-Info, version 7.1.3, the minimum sample size required for the study was calculated to be 85 cases and 85 controls.

In a literature review, the prevalence of gallstones was reported as 11% [2]. With an anticipated population proportion among cases of 11% (and with an absolute precision of 5% at 95% confidence interval and power 80% and to increase the power of the study and increase the statistical power of the study doubling the number of both cases and controls was decided.

Cases were pregnant women with diagnosed gallstone (170) and controls were (170) age matched pregnant women without gallbladder disease attending antenatal care at both Ain Shams Obstetrics and Gynecology University Hospital and *Obstetrics and Gynecology department* at Mansoura University Hospital during the period from 1st of May, 2012 to 1st of June, 2014. The study was approved by the ethical committee of both Ain Shams faculty of Medicine and Mansoura Faculty of Medicine and all women gave informed consent.

2.3 Data Collection

Both cases and controls were subjected to the following:

2.3.1 Questionnaire and physical examination

For each subject a comprehensive questionnaire was completed covering the following parameters: Socio-demographic information; age, sex, residence (urban/rural), education, occupation, number of previous pregnancies, previous use of oral contraceptive pills (OCP), past history of gallbladder stones and family history of gallstone disease. Social score was modified and calculated according to El-Sherbini and Fahmy [14].

The questionnaire included questions on the level of physical activity at work, hours per day of walking, home/household work, leisure-time activity/inactivity and sleeping and the physical activity levels were measured as metabolic equivalents (METs)/hour/day and were scored into mild (<3.0 METs or <4 kcal/min), moderate (3.0-6.0 METs or 4-7 kcal/min) and hard or vigorous (>6.0 METs or >7 kcal/min) [15].

Dietary intake behavior was assessed using a 70-items semi-quantitative food frequency

questionnaire. The questionnaire is an updated and extended version of a previously validated 61-item version [16]. For each of the 70 food items listed, participants are asked to estimate their use of that food in terms of a standard portion size. Participants report the frequency of consumption of each food by selecting one of nine frequency categories. The questionnaire includes a write-in section for foods not listed and for the exact brand of margarine and type of fat used for frying, cooking, and baking.

Nutrient intakes were calculated from the questionnaire by multiplying the portion size consumed by of each food by its nutrient composition to obtain a total nutrient intake for each individual particularly total energy, total fat, saturated and polyunsaturated fat, cholesterol and carbohydrates. The average daily nutrient intake for the three days was determined. The software program, ESHA was used to analyze the nutrient content of the diet consumed by subjects under study after supplements with information about Egyptian dishes were loaded in the program after referring to its ingredients. An average intake per day was estimated about the intake of food producing energy, protein, carbohydrates, fat saturated fatty acid (SFA), monounsaturated fatty acid (MUFA) and poly-unsaturated fatty acid (PUFA), dietary fiber, and basic food groups (for example, cereals, vegetables, fruits, milk-bean products).

Based on the recommendations of the WHO for anthropometric measurements, patients then underwent determination of body height and weight. BMI was calculated according to the common formula [17].

2.3.2 Ultrasound examination

Upper abdominal ultrasonography examination was performed for each participant for the evaluation of gallstone disease. Study participants were asked to attend for the examination following a 6-h fasting period.

Ultrasound examinations were performed with a standard imaging protocol by a group of 5 examiners trained in gallbladder sonography. These examiners worked under the supervision of an experienced specialist who also reviewed any questionable findings. Examinations were performed using a 3.5- to 7.0-MHz convex scanning transducer, SonAce ultrasound scanners (Samsung Medison Co., Ltd. Seoul, South Korea).

The gallbladder was examined in three planes (longitudinal, cross-sectional and diagonal), providing the examiner with a three-dimensional impression of the organ. In cases in which cholecystolithiasis was present, the number, size, localization of stones and the mobility of the stone(s) were assessed. The thickness of the gallbladder wall was measured.

Criteria for the diagnosis of gallstones were as follows: Stones were defined as high-level echoes larger than 2 mm in diameter with post-acoustic shadowing. Sludge was defined as low-level echoes without post-acoustic shadowing which shifted by a change in position.

2.3.3 Blood bio-chemical investigation

Blood samples were collected after an overnight fast to estimate cholesterol, triglycerides, LDL-C, HDL-C, Glucose, cholesterol, triglycerides; LDL-C and HDL-C concentrations. Lipid profile and glucose were measured using commercially available kits supplied from BioMereux (France).

2.4 Data Analysis

Data were analyzed using Epi Info version 7.1.3, Variables were presented as number and per cent. Chi squared test and t-test were used for comparison between groups. Odds ratio (OR) and their 95% confidence (CI) were calculated. P-values less than 0.05 were considered statistically significant.

3. RESULTS

Both cases and controls were age matched where there was no statistical significant difference between them as regards age. Significant statistical difference was found between cases and controls as regards education, occupation, income and social score. Illiteracy was the highest risk (OR=14.3) followed by just reading and writing (OR=12.5) followed by insufficient income (OR=10.6) followed by non working (OR=3). Three fold increase (OR=3) was among low social score Table 1.

Significant statistical difference was found between cases and controls as regards family history of gall stones, parity ≥3 and previous hormonal contraception. Previous hormonal contraception was the highest risk (OR=7.9) followed by family history of gall stones (OR=4.2) and parity ≥4 (OR=3.8) Table 2.

Table 1. Socio-demographic characteristics of study participants

Characteristic	Cases (pregnant women with gallstones)	Controls (pregnant women without gallstones)	Significance test	OR (95%CI)*
Age	**N (%)**	**N (%)**		
< 20 -25	3 (1.8)	4 (2.4)		
25 -30	70 (41.2)	68 (40)		
30 -35	89 (52.3)	85 (50)	$\chi 2 = 13.6$, P=0.6	-
>35 years	8 (4.7)	13 (7.6)		
Education level				
High education	5 (2.9)	25 (14.7)		1(r)
Secondary	70 (41.2)	110 (64.7)	$\chi 2 = 5.5$, P=0.01	3.2(1 -10)
Read & write	35 (20.6)	14 (8.2)	$\chi 2 = 22.3$, P<0.001	12.5(3.6-46.8)
Illiterate	60 (35.3)	21 (7.4)	$\chi 2 = 29.7$, P<0.001	14.3(4.4-49.2)
Occupation				
Working	38 (22.4)	78 (45.9)		1(r)
House wife	132 (77.6)	92 (54.1)	$\chi 2 = 20$, P<0.001	3(1.8-4.8)
Income				
Save money	29 (17.1)	57 (33.5)		1(r)
Sufficient	60 (35.3)	98 (57.7)	$\chi 2 = 1.2$, P=0.5	1.2(0.7-2.2)
Insufficient	81 (47.6)	15 (8.8)	$\chi 2 = 48.7$, P<0.001	10.6(5-23.1)
Social score				
High	65 (38.2)	77 (45.3)		1(r)
Middle	50 (29.4)	71 (41.8)	$\chi 2 = 0.5$, P=0.4	0.8(0.5-1.4)
Low	55 (32.4)	22 (12.9)	$\chi 2 = 13.3$, P<0.001	3(1.6-5.6)

Table 2. Comparison between cases and controls as regards reproductive characteristics and family history of gallstone disease

Characteristic	Cases (pregnant women with gallstones)	Controls (pregnant women without gallstones)	Significance test	OR (95%CI)*
	N (%)	**N (%)**		
family history of gall stone disease				
No	83 (48.8)	136 (80)		1(r)
Yes	87 (52.2)	34 (20)	$\chi 2 = 36$, P<0.001	4.2(2.5-7)
Parity				
1	13 (7.6)	25(14.7)		1(r)
2	39 (23)	66 (38.8)	$\chi 2 = 0.1$, P=0.7	1.1(0.5-2.7)
3	51 (30)	45(26.5)	$\chi 2 = 3.9$, P<0.05	2.2(0.9-5.1)
≥4	67 (39.4)	34(20)	$\chi 2 = 11.7$, P<0.001	3.8(1.6.9)
Previous hormonal contraception				
No	72 (42.3)	145(85.3)		1(r)
Yes	98 (57.7)	25(14.7)	$\chi 2 = 67.9$, P<0.001	7.9(4.6.13.8)

Regarding body mass index, nutritional behavior and physical activity, significant statistical differences were found between cases and controls. The risk of gall bladder stone disease increases by increase in body mass index (OR=5 and 12.8 with BMI 25-29 and ≥ 30 kg/m^2 respectively assuming OR=1for BMI <25). The highest risky nutritional behaviors respectively were; the preference of fried meals (OR=41.3), taking more than two food servings rich in animal fat per day (OR=38.9),the habit of eating eastern sweets ≥twice weekly (OR=18.7), food intake between meals (OR=14), night eating (OR=8.7), taking more than two sugary beverages/day (OR=7.3), eating more than three meals/day (OR=3),

taking more than five sugar teaspoonfuls/day (OR=3), eating more than two rice servings/day (OR=2), eating more than three breads/day (OR=2).The highest risky physical activity score was light physical activity (OR=4.1) Table 3.

Higher mean daily nutrient intakes of total energy, proteins, carbohydrates, total fat, cholesterol, table sugar, saturated fat were significantly higher among pregnant women with gallstone disease than controls while monounsaturated fat, polyunsaturated fat, dietary fiber, potassium, calcium, iron and vitamin C were significantly higher among pregnant women without gallstone disease. No statistical significant difference was found between cases and controls regarding vitamin A, vitamin B1 and vitamin B2. Regarding lipid profile; higher levels of serum total cholesterol, triglycerides and serum LDL-C were significantly higher among pregnant women with gallstone disease than controls while serum HDL-C levels were significantly higher among pregnant women without gallstone disease than cases Table 4.

4. DISCUSSION

In Egypt**,** during the last few decades, the frequency of gallstone disease among pregnant women is increasing. This work showed that threefold increase was among low social score. Social class is an indirect measure of many factors characteristic of different ways of life.

There is evidence that the use of oral contraceptives increases the cholesterol saturation of bile possibly alters gallbladder function, which could produce gall-bladder disease [6]. The correlation between hormonal contraception use and gallstones has been shown in a number of previous studies [5-8]. The current study showed that previous hormonal contraception was the highest reproductive risk factor while parity exerted a moderate risk. Both the frequency and number of pregnancies are strongly associated with higher risk for biliary sludge or gallstones [5,7,8]. Family history of gall stones was a moderate risk factor coinciding with several epidemiological and family studies suggest a strong genetic component in the causation of this disease [2,4].

Body mass indices (BMIs) were significantly higher in the pregnant women who experienced gallstone disease than in those who did not have gallstone disease, the risk of gallstone disease increases by increase in body mass index (OR=12.8 for≥ 30 kg/ m^2). Several studies coincide with finding [3,5] this may be explained by the metabolic consequences of obesity syndrome which is a consequence of obesity. Physical activity was significantly lower among women with gallstone disease, the highest risky physical activity score was light physical activity (OR=4.1). Sedentary lifestyle is a risk factor for obesity and many chronic diseases.

Most women with gallstone disease in this study significantly practiced faulty risky nutritional behaviors as the preference of fried meals, taking more than two food servings rich in animal fat per day, the habit of eating eastern sweets ≥ twice weekly, food intake between meals, night eating, taking more than two sugary beverages/day, eating more than three meals/day, taking more than five sugar teaspoonfuls/day, eating more than two rice servings/day, eating more than three breads/day. In general, from the literature ecological comparisons offer indirect evidence that diet may be an important factor in gallstone development and higher prevalence rates of gallstone disease in westernized than in non-westernized countries had been reported [9,18]. Positive associations have also been found for fried food consumption and gallstone disease [19].

Excessive energy, total fat, cholesterol, table sugar, saturated fat intake were significantly higher among pregnant women with gallstone disease. This may be primarily explained by contributing to obesity [9]. Insoluble fiber may protect against gallstone occurrence by speeding intestinal transit and reducing the generation of secondary bile acids such as deoxycholate, which has been associated with increased cholesterol saturation of the bile [20]. From the present work, significant higher mean daily nutrient intakes of monounsaturated fat, polyunsaturated fat, dietary fiber, vitamin C were among pregnant women without gallstone disease than cases. Dietary factors that may prevent the development of gallstones include polyunsaturated fat, monounsaturated fat, fiber and vitamin c, calcium and iron [9,21].

Higher levels of serum total cholesterol, triglycerides and serum LDL-C were significantly higher among pregnant women with gallstone disease than controls while serum HDL-C levels were significantly higher among pregnant women without gallstone disease than cases. Significant correlation of serum total cholesterol, triglycerides and serum LDL-C and biliary lipoproteins which may play a critical in the formation of gallstone had been reported,

Table 3. Comparison between cases and controls regarding body mass index, nutritional behavior and physical activity

Characteristic	Cases (pregnant women with gallstones)	Controls (pregnant women without gallstones)	Significance test	OR (95%CI)
	N (%)	N (%)		
Body mass index (kg/ m^2)				
< 25	34(20)	104(61.2)		1(r)
25 – 30	90(52.9)	55(32.3)	$\chi2$ = 40.2, P<0.001	5(2.9-8.7)
≥ 30	46(27.1)	11(6.5)	$\chi2$ = 52.5, P<0.001	12.8(5.6-29.6)
Number of regular meals/day				
≤ 3	67(39.4)	114(67.1)		1(r)
> 3	103(60.6)	56(32.9)	$\chi2$ = 26.1 ,P<0.001	3.1(2-5)
Food intake between meals				
No	44(25.9)	141(82.9)		1(r)
Yes	126(74.1)	29(17.1)	$\chi2$ = 111.6 ,P<0.001	14(8-24.5)
Number of bread /day				
≤ 3	59(34.7)	105(61.8)		1(r)
> 3	111(65.3)	65(38.2)	$\chi2$ = 8.4 ,P<0.01	2 (1.2-3.2)
Number of rice serving/day				
≤ 2	98(57.6)	124(72.9)		1(r)
> 2	72(42.4)	46(27.1)	$\chi2$ = 8.8 ,P<0.01	2 (1.2-3.2)
Number of sugar teaspoonful/day				
≤ 5	64(37.6)	109(64.1)		1(r)
> 5	106(62.4)	61(35.9)	$\chi2$ = 23.8,P<0.001	3(1.9-4.8)
Number of food servings rich in animal fat/day				
≤ 2	24(14.1)	147(86.5)		1(r)
> 2	146(85.9)	23(13.5)	$\chi2$ = 178,P<0.001	38.9 (20.1-75.9)
Number of sugary beverages/day				
≤ 2	25(14.7)	96(56.5)		1(r)
> 2	145(85.3)	74(43.5)	$\chi2$ = 64.7 ,P<0.001	7.5(4.3-13.1)
Preference of fried meals				
No	15(8.8)	136(80)		1(r)
Yes	155(91.2)	34(20)	$\chi2$ = 174 ,P<0.001	41.3 (20.6-83.9)
Habit of eating of eastern sweets				
Occasionally	23(13.5)	74(43.5)		1(r)
Monthly	64(37.7)	81(47.7)	$\chi2$ = 10.5 ,P<0.001	2.5(1.4-4.7)
≥Twice weekly	83(48.8)	15(8.8)	$\chi2$ = 73.1 ,P<0.001	17.8(8.2-39.4)
Night eating				
No	23(13.5)	98(57.6)		1(r)
Yes	147(86.5)	72(42.4)	$\chi2$ = 72.2 ,P<0.001	8.7(4.9-15.4)
Physical activity score				
Hard/Vigorous	12(7.1)	22(12.9)		1(r)
Moderate	43(25.3)	96(56.5)	$\chi2$ = 0.2 ,P=0.6	0.8(0.4-1.9)
Light	115(67.6)	52(30.6)	$\chi2$ = 13.7 ,P<0.001	4.1(1.8-9.5)

**OR=Odds Ratio, CI=Confidence Interval; (r) = reference group*

Table 4. Comparison between cases and controls as regards mean daily nutrient intakes and laboratory serum lipid profile

Daily nutrient intakes	Cases (pregnant women with gallstones)	Controls (pregnant women without gallstones)	Significance test
	X±SD	X±SD	t, p values
Total energy (kcal)	2786±189	2137±54	43.1, <0.001
Proteins (gm)	123±28	103±11.5	8.6,<0.001
Carbohydrates (gm)	424.2±1.4	357.2±1.1	490.7,<0.001
Table Sugar (gm)	87.7±24.2	65.7±10.1	10.9,<0.001
Total fat (gm)	92.2±13.1	73.7±2.1	18.2, <0.001
Cholesterol (mg)	396±73.3	304±15.6	16, <0.001
Saturated fat (gm)	29.6±6.7	18.3±1.3	21.6, <0.001
Monounsaturated Fat (gm)	24.9±3.4	43.9±4.1	-46.5,<0.001
Polyunsaturated fat (gm)	11.9±1.3	18.1±1.8	-36, <0.001
Dietary fiber	22.8±3.5	29.9±11.3	-7.8, <0.001
Potassium (mg)	3226±465.2	3427±583.1	-3.5, <0.001
Sodium (mg)	1799±253.6	1583±234.6	8.1, <0.001
Calcium (mg)	461.5±63.1	556.2±159.2	-7.2, <0.001
Iron (mg)	16.1±3.2	19.3±3.7	-8.5, <0.001
Vitamin C (mg)	145.0±31.0	176.0±37.2	-8.3, <0.001
Vitamin B2 (mg)	2.36±0.74	2.29±0.41	1.1, =0.3
Vitamin B1 (mg)	1.58±0.36	1.53±0.42	1.2, =0.2
Vitamin A (µg)	2371±612.5	2361±580.0	0.16, =0.8
Laboratory lipid profile(mg/dl)			
Serum total cholesterol	227±58	187±47	7,<0.001
Serum Triglycerides	214±61	159±49	9.1,<0.001
Serum LDL-C	138±48	121±32	3.8,<0.001
Serum HDL-C	36.9±7	42±12	-4.8, <0.001

conversely HDL-C may exert a protective effect against gallstone formation in gallbladder [22,23].

5. CONCLUSION AND RECOMMENDATION

Multiple risk factors were found among pregnant women with gallstone disease as low socioeconomic standard, family history of gall stones, parity ≥3, previous hormonal contraception, increase in body mass index, light physical activity, risky nutritional behaviors. Most of the risk factors are modifiable as dietary risk factors, overweight and obesity should be controlled, encouraging physical activity and optimizing hormonal contraception practice when indicated. Adequate intake of monounsaturated fat, polyunsaturated fat, dietary fiber, potassium, calcium, iron and vitamin C may have a protective effect against gallstone formation.

CONSENT

All authors declare that 'verbal informed consent was obtained from the participants.

ETHICAL APPROVAL

The study protocol was approved by the ethical committee of Mansoura faculty of medicine.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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