Pregnancy is not a risk factor for gallstone disease: Results of a randomly selected population sample

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Abstract

AIM: To investigate the prevalence, risk factors, and selection of the study population for cholecystolithiasis in an urban population in Germany, in relation to our own findings and to the results in the international literature.

METHODS: A total of 2 147 persons (1 111 females, age 42.8 ± 12.7 years; 1 036 males, age 42.3 ± 13.1 years) participating in an investigation on the prevalence of Echinococcus multilocularis were studied for risk factors and prevalence of gallbladder stone disease. Risk factors were assessed by means of a standardized interview and calculation of body mass index (BMI). A diagnostic ultrasound examination of the gallbladder was performed. Data were analyzed by multiple logistic regression, using the SAS statistical software package.

RESULTS: Gallbladder stones were detected in 171 study participants (8.0%, n = 2 147). Risk factors for the development of gallbladder stone disease included age, sex, BMI, and positive family history. In a separate analysis of female study participants, pregnancy (yes/no) and number of pregnancies did not exert any influence.

CONCLUSION: Findings of the present study confirm that age, female sex, BMI, and positive family history are risk factors for the development of gallbladder stone disease. Pregnancy and the number of pregnancies, however, could not be shown to be risk factors. There seem to be no differences in the respective prevalence for gallbladder stone disease in urban and rural populations.

Key words: Cholecystolithiasis; Pregnancy; Risk factors; Selection bias; Ultrasonography

INTRODUCTION

Disorders of the gallbladder are a major cause of morbidity and a leading indication for hospital admissions in the United States[1-4] and in Europe[5,6]. In these developed nations, the economic impact of gallstone disease is high[1-3]. In the United States, more than 500 000 cholecystectomies are performed annually and direct costs for the diagnosis and treatment of gallbladder stones are estimated at 5 billion US Dollar per year[7,8]. For the treatment of gallstone disease in Germany, 200 inpatient hospital days per 10 000 health insured persons accumulate every year[9]. This creates costs of more than ½ billion[10]. Gallstone disease is not only an unsolved problem in Western industrialized nations but also in African nations[11,12] as well as in Asian countries like China, India, Bangladesh, and Japan[13-17]. Cholelithiasis is one of the commonest surgical diseases in China and accounted for 11.5% of overall hospitalized patients during the period from 1985 to 1995[18].

The most important risk factors for the development of gallstone disease currently being discussed in the literature include age[19-23], female gender[14,20-22,24], obesity[26,27] and heredity[25,20,33]. Other factors like pregnancy or number of pregnancies are still discussed are contradictory[21,32,34].

To our knowledge, there are no publications that assess the influence of the selection of study population on gallstone disease prevalence.

The present prospective ultrasound-based survey investigates the prevalence and risk factors for cholecystolithiasis in an urban population and also addresses the effect of selection of study population on the different risk factors.
Study collective and participation

A random sample of 4 000 subjects was selected from the population of a city in southwestern Germany (total population: 12 475) for participation in a seroprevalence study for *Echinococcus multilocularis*. Of the 4 000 randomly selected and invited subjects, 107 could not be included in the final evaluation due to factors such as non-response to repeated invitations or incompetent legal status (n = 39), or moved away with no forwarding address (n = 68), resulting in a total random sample size of 3 893 subjects. Out of this pool, a total of 2 445 persons actually participated in the study (response rate: 62.8%). The following inclusion and exclusion criteria determined the composition of the collective studied for gallbladder stone disease (Figure 1):

Only persons in the age of 10-65 years were included into the study. Written consent for the examination and collection of personal health information was required.

Failure to visualize and assess the gallbladder or poor or restricted examination conditions lead to the exclusion from the study collective (n = 26 subjects). Significant contraction of the gallbladder following an inadequate fasting period (when no clinical signs of cholecystitis were identified) (n = 9 subjects), a history of cholecystectomy for gallbladder polyps or cholecystectomy of unknown reason (n = 4 subjects) or subject's refusal to undergo examination (n = 1 subject) also constituted exclusion criteria. Missing or invalid data acquisition (n = 4 subjects). Patients with prior cholecystectomy for gallbladder stones were added in the calculations of the gallbladder stone prevalence.

The total collective of subjects undergoing ultrasound examination of the gallbladder was 2 401 persons. In order to enhance comparability with published studies, we explicitly examined adult subjects aged 18-65 years. This non-selected adult collective consisted of 2 147 subjects (1 036 males, 48.3%; 1 111 females, 51.7%).

Subjects' informed written consent was obtained for examination and collection of personal health information. The study met the international agreements of the Helsinki Declaration from 1996 and was approved by the research Ethics Committee of the Baden-Württemberg General Medical Council (Landesärztekammer Baden-Württemberg).

Questionnaire and physical examination

Under the guidance of a trained interviewer, each subject completed a comprehensive questionnaire covering the following parameters: Demographic information (age, sex, nationality, marital status, education, occupation), recreational activities (sports, exercise), medical history (gallbladder stones, gastrointestinal, hepatic, cardiovascular, respiratory, endocrine, renal, rheumatic, or malignant diseases), dietary behavior (meal patterns including intake of certain foods; fluid intake including alcohol, use of tobacco products), family history (gall bladder stone disease, diabetes mellitus, overweight, history of cancer) and medication history.

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

Ultrasound examination

Study participants were asked to present for the examination following a 4-h fasting period. All subjects underwent ultrasound examination of the upper abdomen under standard conditions to assure exact evaluation of the gallbladder. In order to enhance visualization of the gallbladder, subjects were asked to raise their right arm over their head, which increases both the intercostal spaces and the distance between the lower margin of the rib cage and the iliac crest. Examination was performed upon deep inspiration and with outward pressure on the abdominal wall.

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 mobility of the stone(s) was assessed. Subjects, in whom differentiation between mobile stones and wall-adhering polyps was difficult, were examined again in standing position in order to reliably distinguish between stone and polyps on the basis of their mobility. The thickness of the gallbladder wall was measured and, in subjects with gallbladder stones, the number, size, and localization of stones before mobilization were determined. Ultrasound examinations were performed by a group of six examiners trained in gallbladder sonography. These examiners worked under supervision of an experienced specialist (>4 000 examinations per year), who also reviewed all questionable findings. Examinations were performed using four identical, state-of-the-art HDI-5000 ultrasound scanners (Advanced Technology Laboratories Ultrasound, Philips Medical Systems, Bothell, WA, USA).

Criteria for the diagnosis of gallstones were as follows: one or more hyperechoic structure(s) in the gallbladder with dorsal shadow; one or more hyperechoic structure(s) in the gallbladder without dorsal shadow but which by means of examination in multiple planes and/or attempt at mobilization can be certainly distinguished from a gallbladder septum, Heister's valve or a gallbladder polyp; a strongly hyperechoic structure with dorsal shadow in...
the anatomic location of gallbladder, with no or only slight visualization of residual gallbladder lumen; failure to delineate the gallbladder lumen in patients who have undergone prior cholecystectomy and who demonstrate corresponding surgical incisions in the right upper abdominal quadrant; presence of a significant amount of gallbladder sludge filling at least one-quarter of the gallbladder lumen with corresponding dorsal shadow.

Subjects, who because of recent food intake or other reasons, such as overlying intestinal gas, presented unfavorable examination conditions, were excluded from the study.

**Statistical analysis**

Multiple logistic regression \(^{[16]}\) was performed to assess the impact of the known risk factors age, sex, BMI, and positive family history on the development of gallbladder stones. Two further multiple logistic regression models were fitted for female study participants in order to assess the impact of pregnancy and number of pregnancy, whereby in both models odds ratios were adjusted for the known risk factors like age, BMI, and positive family history for gallbladder stones. Odds ratios with 95% confidence interval and corresponding P-value are given. Statistical analyses were performed using the SAS statistical software package (version 8.02).

**RESULTS**

**Prevalence in relation to age and sex**

Gallbladder stones were detected at upper abdominal ultrasound examination in 87 of 2 147 subjects examined (4.1%), while gallbladder sludge was identified in two subjects (0.1%). A further 84 subjects (3.9%) had undergone prior cholecystectomy for the treatment of gallbladder stone disease. Thus, 171 subjects satisfied the inclusion criteria for cholecystolithiasis, representing an overall prevalence of cholecystolithiasis of 8.0% in the study population.

Among females, the proportion of subjects with current or prior gallbladder stone disease stood at 10.9% (121 of 1 111 subjects), while 4.8% of males (50 of 1 036 subjects) fulfilled the criteria for the diagnosis of cholecystolithiasis. The prevalence of gallbladder stone disease was higher for females than for males in all age classes. The highest prevalence was found in the group of females aged 51-65 years (20.9%; 73 of 349 subjects; Figure 2). Overall, the prevalence of gallbladder stones (defined as current and past cholecystolithiasis) increases with advancing age from 1.5% among subjects aged 18-30 years to 15.2% in the 51-65 years age group.

**Prevalence in relation to BMI**

BMI was calculated in 99.6% of study participants \( (n = 2 138) \). Mean BMI for the subcollective of subjects without gallbladder stone disease was 25.8±4.9 kg/m\(^2\) (median 25.1 kg/m\(^2\); range: 14.1-52.6 kg/m\(^2\)). Corresponding value for subjects with current or prior cholecystolithiasis was 29.2±5.9 kg/m\(^2\) (median 28.7 kg/m\(^2\); range: 17.6-51.5 kg/m\(^2\)). For description, BMI results were assigned to one of three classes defined according to the recommendations of the World Health Organization (WHO; Figure 3).

Class I, defined as at or below a subject’s respective ideal weight \( (\text{BMI}<21 \text{ kg/m}^2 \text{ in females and } <22 \text{ kg/m}^2 \text{ in males}) \), included 367 subjects (17.2%). Class II (BMI 21-25 kg/m\(^2\) in females and 22-26 kg/m\(^2\) in males) included 804 subjects (37.6%), while 967 subjects (45.2%) met the criteria for Class III (BMI >25 kg/m\(^2\) in females and BMI >26 kg/m\(^2\) in males), and thus were considered as overweight. Only 9 subjects (2.5%) in BMI Class I exhibited evidence of gallbladder stone disease compared to 37 subjects (4.6%) in Class II and 124 subjects (12.8%) in Class III (Figure 3).

**Prevalence in relation to positive family history of gallbladder stones**

Of 2 147 subjects, 105 (4.9%) were unable to provide information on their biological parents; thus, evaluation of the influence of hereditary predisposition was limited to a subcollective of 2 042 subjects. Gallbladder stones were diagnosed more frequently in subjects with a positive family history of cholecystolithiasis. In subjects with a positive family history involving one biological parent, the prevalence of gallbladder stones stood at 12.6% (51 of 405 subjects) and at 14.3% (3 of 21 subjects) in subjects, both of whose biological parents suffered from gallbladder stone disease. In the remaining 1 616 subjects with negative family history of gallbladder stone disease, prevalence of cholecystolithiasis stood at only 6.3% \( (n = 102) \).
Classical risk factors of cholecystolithiasis in multiple logistic regression

| Classical risk factors | Odds ratio (OR) | 95%CI       | P     |
|-----------------------|----------------|------------|-------|
| Age (per yr)          | 1.06           | 1.05-1.08  | <0.001|
| Female sex            | 2.78           | 1.91-4.07  | <0.001|
| BMI (per kg/m²)       | 1.12           | 1.08-1.15  | <0.001|
| Positive family history| 1.89           | 1.30-2.75  | <0.001|

Table 2 History of pregnancy and the number of prior pregnancies in the multiple logistic regression model (only females)

| Factor tested                  | Odds ratio (OR) | 95%CI       | P     |
|--------------------------------|----------------|------------|-------|
| Age (per yr)                   | 1.06           | 1.04-1.08  | <0.001|
| BMI (per kg/m²)                | 1.11           | 1.07-1.15  | <0.001|
| Positive family history        | 1.99           | 1.28-3.07  | 0.002 |
| Positive history of pregnancy  | 0.76           | 0.44-1.31  | 0.321 |

Prevalence in relation to pregnancy

All female study subjects were questioned about their pregnancy status. Fifteen women declined to provide information on prior pregnancy. Of the remaining 1,096 subjects included in this analysis, 26.3% (n = 288) reported never having been pregnant. The group of women with positive history of pregnancy (n = 808, 73.7%) was broken down into the group with one to two pregnancies (560 women, 51.1%) and those with three or more pregnancies (248 women, 22.6%). Gallbladder stones were detected in 22 of 288 nulliparae (7.6%). In the group of 560 women with one or two pregnancies, 55 subjects (9.8%) were positive for past or present cholecystolithiasis, compared to 43 subjects (17.3%) in the group of patients with three or more pregnancies.

Multiple logistic regression analysis

Multiple logistic regression showed a strong association of the factor “age” with the development of gallbladder stones (OR 1.11 per year of age; 95%CI: 1.05-1.08; P<0.001; Table 1). The comparison of females to males yielded an odds ratio of 2.78 (95%CI: 1.91-4.07; P<0.001; Table 1). Body mass index (BMI in kg/m²) also was an important risk factor (OR 1.12 per-unit; 95%CI: 1.08-1.15; P<0.001; Table 1). Compared to study subjects without known gallbladder stone disease in the biological parents, persons with a positive parental history of cholecystolithiasis showed an odds ratio of 1.89 (95%CI: 1.30-2.75; P<0.001; Table 1).

In separate logistic regression models for females including the risk factors age, BMI, and family history, neither pregnancy nor number of pregnancies showed an association with the development of gallbladder stone disease. The first model revealed an OR of 0.76 for pregnancy yes vs no (95%CI: 0.44-1.31; P = 0.321; Table 2) and the second model an OR of 0.65 for one or two pregnancies vs no pregnancy and an OR of 1.04 for three or more pregnancies vs no pregnancy (95%CI: 0.37-1.15 and 0.56-1.94; P = 0.104; Table 3).

DISCUSSION

The present ultrasound-based epidemiological survey is, to our knowledge, the first study conducted in a collective drawn from an urban population in Germany. The prevalence of gallbladder stone disease in our unselected collective stands at 8.0%. Our findings are comparable, on one hand, with those documented in a rural population and in a collective of blood donors in Germany,[19,20] and, on the other, with the prevalence figures reported from Italian, British, and Danish studies,[14,16,17,23,38], but our results are not comparable with the low prevalences from Eastern countries such as China, India, Japan, Taiwan, and Thailand.[4,10,17,23,38] (Figure 4).

The prevalence of gallbladder stone disease (predominantly cholesterol gallstones) reported from a majority of European and American studies shows a clear female dominance. In Asian countries with a higher prevalence of pigment gallstones, the female dominance is less distinct.[6,23,38] In the present study, female sex was also found to be a clear risk factor (OR = 2.78; 95%CI: 1.91-4.07; P<0.001) and the ratio of males with gallbladder stone disease to females stood at 1 to 2.3. Due to the great importance of the risk factors, age and especially female sex, the selection modalities of study collectives gain paramount importance.[6,23,38]. Comparing gallbladder stone prevalence in women in relation to the method of selecting the study population, the highest prevalence is observed in studies conducted as a cross sectional sample of the total population[19–22] or large random samples[8,23,38] (Table 4). Most large European studies were conducted either as random samples[10,19,20] or as surveys of entire factories or governmental departments[12,41] (Table 4).

Our findings from Leutkirch (total prevalence 8.0%) are comparable to those reported for populations in Römerstein (7.8%) and blood donors in Ulm (6.0%) as well as to Italian studies conducted in Sirmione (6.9%) and Chianciaio (5.9%), all of which were conducted as cross-sectional sample of the total population[19–22] (Figure 4).

The prevalence of gallbladder stones in our study collective is lower in younger persons than in those belonging to older age groups. Similar trends toward higher gallbladder stone prevalence in older persons have been described in nearly all sonographic studies[6,19,20,23,38], as well as in autopsy studies[17] and in studies based on clinical symptoms[41] (Figure 4).

Using multiple regression analysis under consideration...
of the known risk factors age, sex, and family history, we found an association with study participants’ current BMI (OR 1.12/unit; 95%CI: 1.08-1.15; P<0.0001). As in most other European studies, our findings showed an increased prevalence of gallbladder stone disease in overweight subjects[6,25-28]. The prevalence of gallbladder stones in subjects with a positive family history in the biological parents (12.7%) is more than twice as high as that in subjects with negative family history (6.3%). Our findings point to a strong effect for genetic factors in the pathogenesis of cholecystolithiasis (OR = 1.89; 95%CI: 1.30-2.75; P<0.001), although the mechanism of inheritance is not known. A familial accumulation of cholecystolithiasis cases has been observed in other sonographic screening studies in first-degree relatives of persons suffering from gallbladder stones[6,28-31,39].

The multiple logistic regression model failed to show an increased prevalence of gallbladder stones for female subjects with prior pregnancy (prevalence 12.1% vs 7.6%). One reason might be the much lower average age of the nulliparae (33.6±13.7 years) compared to women who had borne children (46.0±10.7 years), suggesting that the higher prevalence may actually be an age-related phenomenon. This effect is also apparent in the increased prevalence of gallbladder stones in women with three or more pregnancies (average age 48.9±9.7 years) compared with women who had been pregnant only one or two times (average age 44.7±10.9 years). The analysis of pregnancy as a risk factor for cholecystolithiasis has lead to different results in the literature[12,21,32-34] which range from no effect to a prevalence that is reduced by a factor of 40 in comparison of nulliparae to women who have been pregnant[13,43] (Table 5). The old clinical experience of an increased prevalence of gallbladder stones in women who have borne children could not be substantiated by the findings of the present study.

In conclusion, the classical risk factors age, female sex, body mass index (BMI), and positive family history have been confirmed by the findings of the present study. The female-specific factors of prior pregnancy and number of prior pregnancies, however, could not be shown to exert measurable influence on the prevalence of gallbladder stones. The selection of study populations affects study results i.e. the strength of the effect of female sex on the development of gallbladder stones. There does not appear to be a difference between the prevalence of gallbladder stones in urban and rural populations.

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**Table 4 Relative risk for gall bladder stones in relation to selection of study population**

| Place/region | Population selection | n | Sex distribution |
|--------------|----------------------|---|-----------------|
| Chianciano   | Random sample        | 923 | 1:1.0          |
| Rome         | Factory              | 2 325 | 1:1.1          |
| Bergo        | Random sample        | 1 371 | 1:1.1          |
| Ulm          | Blood donors         | 1 116 | 1:1.1          |
| Copenhagen   | Random sample        | 4 807 | 1:1.4          |
| Chiang Mai   | Random sample        | 6 146 | 1:1.5          |
| Schwedt      | Factory              | 1 616 | 1:1.6          |
| Okinawa      | Inhabitants of an island | 2 584 | 1:1.7          |
| Jiaosting    | Random sample        | 15 856 | 1:2.0         |
| M.I.C.O.L.   | Random sample        | 29 739 | 1:2.0         |
| Römerstein   | Total survey         | 2 498 | 1:2.1          |
| Sirmione     | Total survey         | 1 911 | 1:2.2          |
| Cianciano    | Total survey         | 1 804 | 1:2.3          |
| Leutkirch    | Random sample        | 2 401 | 1:2.3          |
Table 5: Review of published studies addressing the effect of the factor “pregnancy” on the prevalence of gallbladder stones

| Factor by which the prevalence of gallstone disease in women with prior pregnancy is increased | 1.0–1.5 times | 1.6–2.5 times | 2.6–10 times | 11–50 times |
|---|---|---|---|---|
| **Studies showing a quantitative relation between cholecystolithiasis and pregnancy** | 1966 Framingham [42] | 1982 Oxford [47] | 1979 Stockholm [46] | 1988 Srinagar [51] |
| | 1988 Sirmione [21] | 1982 Kopenhagen [46] | 1982 Rom [52] | |
| | 1985 San Antonio [46] | 1985 Maastricht [44] | 1986 Schwedt [45] | |
| | 1982 Birmingham [46] | | 1998 Baltimore [46] | |
| **Studies not showing a quantitative relation between cholecystolithiasis and pregnancy** | 1956 Birmingham [56] | 1970 Pima reservation [51] | 1980 Boston [22] | |
| | | | 1982 Oberpfuss [22] | |
| | | | 1983 Oxford [22] | |
| | | | 1984 Adelaide [22] | |
| | | | 1989 Soweto [21] | |
| | | | 1990 Dublin [41] | |
| | | | 1995 Ulm [21] | |
| | | | 1996 Römerstein [21] | |
| | | | 2002 Leutkirch | |

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