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Investigation of Biliary Canal Variations as a Cause of Stone Formation in the Choledochal Canal**Medișoğlu M. Sabri¹, Çolak Tuncay¹, Yalnız Ahmet², Çam İsa³, Sezikli Mesut⁴, Baltrak Y. Atakan⁵**¹Kocaeli University, Faculty of Medicine, Departments of Anatomy, Turkey²University of Health Sciences, Derince Training and Research Hospital, Radiology Clinic, Turkey ³Kocaeli University, Faculty of Medicine, Departments of Radiology, Turkey⁴Hitit University, Çorum Erol OLÇOK Training and Research Hospital, Gastroenterology Clinic, Turkey ⁵University of Health Sciences, Derince Training and Research Hospital, Pediatric Surgery Clinic, Turkey.

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Abstract: The present study aimed to investigate if there is an association between the diameter of the choledochal duct and choledochal duct stone formation. The present study consisted of 79 patients who had endoscopic interventions and MRCP procedure with surgery history. Some followed due to disorders of the liver, gall bladder, and biliary tract and some of whom presented hepatobiliary complaints between 2017 and 2019. The choledochal duct diameter measured from MRCP images and choledochal duct stone had examined; the type classified according to Huang classification. Among the cases classified, 29 patients, was Huang Type A1, 27 patients were Huang Type A2, 16 patients were Huang Type A3, and seven patients were Huang Type A4. There was not any statistically significant association in terms of choledochal diameter regarding the types. Choledochal duct diameter was statistically higher in female patients than male patients ($p < 0.05$). According to the age group, a statistically significant difference detected for choledochal duct stone formation; individuals over 45 years of age present an increase for choledochal duct stone ($p < 0.05$). The choledochal duct diameter was found higher in female patients compared with male patients; stone formation has found increased in both gender over 45 years of age. It should consider before surgical procedures and radiological tests.

Keywords: Biliary tract variations; choledochal diameter; choledochal stone.

INTRODUCTION

Biliary stone disease is a common gastrointestinal problem. Prolongation of the average life period increases the older population; however, an increase in prevalence had also detected due to the changes in nutritional habits¹. Gallbladder stone is one of the most common causes of elective abdominal procedures in general surgery. Although mortality is lower in gall bladder procedures, financial and health effects should consider due to higher morbidity rates. Despite advances in techniques in liver surgeries, biliary complications are a significant cause of morbidity and mortality. It is exceedingly essential to know the anatomical structures very well to reduce mortality and conduct the treatment correctly². Risks in terms of the gallbladder and liver surgery and transplantation surgery, radiologists interpreted

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percutaneous biliary tract drainage anomalies as opaque substance distribution or difficulties in their drainage. If the aim is to increase success and decrease liver operations and transplantation complications, we need to know the anatomy of intrahepatic and extrahepatic bile ducts^{3,4,5}.

Previous studies investigated the relationship between the diameter of the ductus cysticus and the angle between the ductus cysticus and the gallbladder with stone formation. Also, studies investigated the anatomical structures and variational developments^{6,7,8}. Despite these studies' availability, there are no adequate studies in the literature in recent decades regarding the relationships between biliary canal variations and stone formation.

Under the light of these data, we aimed to classify biliary tract formations according to Huang variation types and investigate any possible association between common bile duct (CBD) diameter, CBD stone, and gender as well as age.

MATERIALS AND METHODS

After approval of the Ethical Committee of Kocaeli University with GOKAEK-2018/18. 2018/86 dated and numbered decision, the present study included 79 patients who had endoscopic interventions and MRCP procedure with surgery history. Some of whom followed due to disorders of the liver, gall bladder, and biliary tract and some of whom presented hepatobiliary complaints in Derince Training and Research Hospital within Health Sciences University between 2017 and 2019. After reviewing age, gender, clinical presentation, history of any previous surgery has obtained in 79 patients, CBD diameter and cholelithiasis reviewed on MRCP images in each case. The measurements on the images performed by the same radiologist and taking the same points for measurement considered for each case. CBD diameter had measured from the middle point of the distance from the junction point of the cystic duct (CD) and common hepatic duct (CHD) to ampulla of Vater.

The biliary tract has divided into two-part included intrahepatic and extrahepatic biliary tracts. As identified by Couinaud, the liver consists of eight individual segments with individual portal circulation and venous blood flow¹. It also contains the anatomically segmental structure of the liver. Huang classification has used to classify anatomic variations of the biliary tract. This method is one of the classification methods used for radiological measurements and examinations. Variational states of the biliary tracts were identified and classified differently by the researchers. Couinaud, Champetier, Onkubu, Choi, and Huang made type classifications. Variation classification of the biliary tract is usually done depending on the junction status of the right posterior hepatic duct in general⁹. We used Huang classification in our study. In addition to descriptive statistics, multivariate analysis (binary logistic regression) has used to determine the analytical parameters. P-value<0.05 in multivariate analysis was considered to a significant association.

RESULTS AND DISCUSSION

The participants included 38 females (53.04±19.56 years) and 41 males (54.7±20.75 years). The youngest female patient was 22 years old, and the eldest was 87 years old—the median age value of 56 years. The youngest male case was 19 years old, and the most adult male was 91 years old—the median age value of 58 years.

Classification of anatomical variation of the biliary tract revealed the following; Female patients, 11 (27.5%) patients in Huang A1 type, 20 (50%) patients in Huang A2 type, 5 (17.5%) patients in Huang A3 type, and 2 (5%) patients in Huang A4 type. In the male patients, 18 (43.9%) patients were Huang A1 type, 7 (17.07%) patients were Huang A2 type, 11 (26.8%) patients were Huang A3 type, 5 (12.1%) patients were Huang A4 type.

Accordingly, 29 (36.70%) patients were Huang A1 type, 27 (34.2%) patients were Huang A2 type, 16 (20.3%) patients were Huang A3 type, 7 (8.64%) patients were Huang A4 type.

Table 1. Investigation of the Association Between Variation Type and Common Bile Duct Stone

		Variation Type			P
		A1	A2	A3+A4	
Common Bile Duct Stone	No	20	16	16	0.678
	Yes	9	11	7	
Total		29	27	23	

There was no difference in common bile duct stone according to the various types ($p>0.05$).

Table 2. The Difference Between CBD Diameter and CD -CHD Angle Investigated According to the Age Above and Below 45 Years

Group	Age	N	Mean	Std. Deviation	p
CHD Diameter	45≥	24	5.25	3.86	0.001
	45<	55	8.68	4.71	
CHD-CD Angle	45≥	17	45.17	30.08	0,510
	45<	38	39.34	29.87	

A significant increase detected in CHD diameter over 45 years of age ($p<0.05$). According to the age group, there was no difference detected in the CHD-CD angle ($p>0.05$).

Table 3. Investigation of the Difference for CHD Stone Formation According to the Age Above and Below 45 Years

CHD Stone Present	Age_Group (years)		p
	45> years	45< years	
No	20	32	0,025
Yes	4	23	

A statistically significant difference detected in CHD stone formation according to the age group ($p<0.05$). CHD stone incidence increases in patients over 45 years of age.

Table 4. Analysis of the Association Between CHD-CD Angle and Age as well as CHD

	Age	CHD Diameter	CHD-CD Angle	CHD Stone Dimension
Age		0.00	0.43	0,154
CHD Diameter	0.000		0.106	0.003
CHD-CD Angle	0.434	0.106		0.752
CHD Stone Dimension	0.154	0.003	0.752	

A positive correlation was detected between the age and CHD diameter and between CHD stone dimension and CHD diameter ($p < 0.05$). There was no significant correlation between CHD-CD angle and age and between CHD-CD angle and CHD stone dimension ($p > 0.05$).

Table 5. Comparison of CHD Diameter (mm) According to the Gender

Gender	N	Mean (mm)	Std. Deviation	P
CHD Diameter (mm)	Male 41	6.28	4.15	0.007
	Female 38	9.10	4.91	

Mean CHD diameter was measured 9.1 ± 4.91 mm in female patients and 6.28 ± 4.15 mm in male patients. The mean CHD diameter measured at 7.67 mm.

Table 6. Comparison of Biliary Vesicle Stone Depending on the Gender

Biliary Vesicle Stone Formation	Gender		p
No	Male 23	Female 8	0.005
Yes	10	18	
Operated	8	12	

A significant difference found between female and male groups for biliary vesicle stone depending on gender ($p < 0.05$). The biliary vesicle stone formation was significantly higher in female patients ($p < 0.05$).

The biliary tract may present different anatomic variations both in intrahepatic and extrahepatic locations beyond its normal structure. Biliary tract junction forms may also present different variations; however, the normal anatomic structure has detected in approximately 58% of the global population^{10,11}. Beyond identified anatomic pattern, the biliary tract may present intrahepatic or extrahepatic developmental variations¹²; since such variations may potentially cause problems in surgical procedures in the patients, they may increase the risk of iatrogenic injury during surgical procedures such as open and laparoscopic gall bladder procedures, liver resection or liver transplantation from an alive donor. Different anatomic variations demonstrated to be associated with stone formation, recurrent

pancreatitis, cholangitis, and malignancies^{11,13}. Recognition of all gallbladder variations and possible association of such variations with cholelithiasis is significant to reduce the risks for malpractice and reduce mortality and complication rates.

The present study investigated any possible association between variations of the extrahepatic biliary tract and cholelithiasis. There was no statistically significant association between Huang variation types and cholelithiasis (Table 1). In the present study, any possible correlation between CHD diameter, CHD-CD angle, and CHD stone dimension; consequently, a statistically significant correlation has detected. Another statistically significant output of such correlation was the increase of stone formation in individuals over 45 years of age. Many studies had conducted to search the association between CHD diameter and age, body weight, height as well as BMI. Kaude measured the diameter of the common bile duct on 600 individuals by ultrasound; CHD diameter was 2.8 mm in the individuals below 20 years of age, whereas CHD diameter was measured 4.1 mm in the individuals over 71 years age¹⁴. Recent studies emphasize the effect of aging on CHD diameter. Bachar et al. detected an age-dependent change in CHD diameter by an annual dilatation of 0.04 mm through ultrasound¹⁵. Daradkeh et al. reported that the factors affecting common bile duct diameter were age, cholecystectomy, and BMI¹⁶.

Tom et al. conducted a study on 187 individuals and measured a significant CHD diameter increase by aging¹⁷. Wu et al., Kaim et al., Niederau et al., and Bowie et al. carried out studies about CHD diameter increase by aging and their possible causes¹⁸⁻²¹. Kaim et al. stated that age-dependent increase in CHD diameter might appear due to age-dependent increase of the loss in the reticulo-elastic web and the destruction of longitudinally extending myositis bands and destruction on intermediate connective tissue¹¹. Adibi and Givechian examined the association between CHD diameter and age, BMI, portal vein diameter, and drug addiction; they observed that CHD diameter increases along with wide portal vein in drug addicts in the advanced age²²(Table 2). In the present study, stone formation increased in individuals over 45 years of age (Table 3). Many studies of the literature showed that cholelithiasis prevalence increased by age. Attili et al. reported a linear increase in cholelithiasis and cholecystectomy in both genders by aging²³.

Barbara et al. stated that cholelithiasis' prevalence increases by aging between 18 and 65 years of age²⁴. This is probably because stone formation becomes visible and manifest in the elder ages because of being a gradual and time-taking process. In our study, it measured that individuals with cholelithiasis have increased DCH diameter (Table 4). A statistically significant association of stone formation has observed with CHD diameter increase. This has been explained by the presence of the stone to produce a physical dilatation of the DCH. Boys et al. divided CHD diameter into three groups included 6 mm, 6 to 9.9 mm, and over 10 mm; they measured the diameter smaller in the individuals without CHD stone. In that study, the stone formation rate was 14% in the first and second groups and 39% in the third group²⁵.

The previous studies show differences in anatomic formations where the stone has developed in male and female patients. A significant difference has found in the CHD diameter in MRCP images between female and male patients within this context. The normal range for CHD diameter is 4 to 6 mm; CHD diameter below 5 mm has accepted average whereas a diameter at and above 8 mm is dilated. Mean CHD diameter was measured 9.10 ± 4.91 mm in female patients and 6.28 ± 4.15 mm in male patients. Poralla et al. measured CHD diameter and the pressure inside the

canal in their study in both genders; both CHD diameter and the pressure inside the canal were detected higher in male patients than female patients²⁶. Matcuk et al. reported that CHD diameter is higher in females, and it increases in advanced age and in those who had cholecystectomy in both genders²⁷. The researchers state that cholelithiasis incidence is more in female patients with differences in biliary tract²⁸. This may be expressed with a full CHD diameter in females compared with males (Table 5).

In this study, cholelithiasis rate was statistically higher in female patients than male patients of the present study; the incidence is 2.3-fold higher in female patients (Table 6). Many studies focused on possible risk factors or underlying causes for cholelithiasis among female and male patients. Palermo et al. conducted a research of 1,875 volunteers to investigate the association between cholelithiasis, age, gender, BMI, family history, sedentary life; cholelithiasis incidence was 2.6-fold higher in female volunteers²⁹. Another previous study reported that age, BMI, history of cholic pain, family history, smoking, and hepatosteatoses were all effects on cholelithiasis and radiological anatomy of the biliary vesicle and biliary duct^{30,31}. Yildirim in 2008 conducted a study under the title of "Incidence of cholelithiasis in adults in the province of Tokat and possible risk factors" on 1,095 individuals in Tokat province of our country; he investigated the effect of gender, age, glucose, ALT, AST, total cholesterol, triglyceride, BMI and anthropometric measurements on the frequency of cholelithiasis; he also evaluated anatomic formations and clinical findings through ultrasound. An association has detected between cholelithiasis and female gender, age, fasting glucose, total cholesterol, BMI, triglycerides, and waist circumference³². Some researches reported that stone prevalence in women is 1.7 to 4-fold more than men³³. In our country, Sezer, in 2016, carried out a study with 865 volunteers and detected biliary vesicle stone in 52 volunteers included 41 female individuals³⁴.

Studies indicate that higher cholelithiasis incidence in women may be associated with some factors such as fertility and sex hormones, an increase of estrogen hormone increases cholesterol secretion and causes cholesterol supersaturation³⁵. Some studies suggest that the risk of cholelithiasis increases in women receiving hormone replacement therapy^{36,37}. Some studies demonstrated the association between oral contraceptive use and an increase in the risk of cholelithiasis^{38,39}. A previous study showed that cholesterol and calcium bilirubin crystals in the bile sludge increase by more than 30%⁴⁰. According to the outcomes stated above, gender should consider in the patients presenting colic pain without symptoms of cholelithiasis; furthermore, MRCP images show that CHD diameter may be more comprehensive in women when compared with men, which may increase the rate of small stone accumulation and stone formation in the biliary vesicle. Consideration of possible dilatation in CHD diameter by aging reveals that age may be a determinant factor in CHD diameter and stone formation in MRCP or radiological images.

This study is a retrospective study and had done with the measurements made on the images previously taken in the hospital. Limitations in this study have been that the available figures are not of the desired quality, and the number of patients is low. The lack of previous studies on this subject is one of the limitations of our research.

CONCLUSION

Review of the findings of the present study and literature information, a full CHD diameter may not necessarily indicate a stone; further studies will need to investigate the effect of CHD stone existence on gender, and the impact of age on diameter increase.

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CONFLICT OF INTEREST

The author report no conflicts of interest and no funding resources in this study.

REFERENCES

1. Gazelle G.S, Lee M.J, Mueller PR, Cholangiographic segmental anatomy of the liver. *Radiographics* 1994;14:1005-1013.
2. Sin L.Y, Kuang T.P, Sung Y.C, Ming Y.H, Chien M.C, Chien F.H, Jeng H.T Common and Rare variants of Biliary Tree: Magnetic Resonance Cholangiographic Findings and Clinical Implications, *J.Radiol Sci*, 2012; 37(2):59-67.
3. Jin C.W,Tae K.K,Kyoung W.K,Pyo N.K Hyun K.H, Moon-gyu L, Anatomic variations in intrahepatic bile ducts: an Analysis of Intraoperative Cholangiograms in 300 Copnsecutive Donors for Living donor Liver Transplantation. *Korean J Radiol*. April-June 2003; 4(2):85-90
4. Huang TL, Cheng YF, Chen TY, Chen TL, Lee TY. Variations of the bile ducts: clinical application in the potential donor of living-related hepatic transplantation.*Clin transplant* ,1997;11:337-340.
5. Nery JR, Fraguilidis GP, Scagnelli T, et al. Donor biliary variations: an overlooked problem? *Clin Transplant* ,1997; 11:582-587).
6. Sanal B, Korkmaz M, Zeren S, Can F, Elmalı F, Bayhan Z, Does gallbladder angle affect gallstone formation? *Pan Afr Med*, 2016 Jun 27; 24:165.
7. Jin S.P, Don H.L, Jun H.L, Seok J, Young S.J, *World J Gastroenterol*, 2015 Jan 7; 21(1):276-82;
8. J.Resurreeıçao, L Batista, J.T Soares, I Marques, E Matos, L.Andrade, A.almeida, et all. Normal anatomy and anatomic variants af the biliary tree and pancreatic ductal system at MRCP- what clinicians want to know ECR 2014,educational exhibit, Poster No: C-1696)
9. Hyodo T, Kumano S, Kushihata F, Okada M, Hirata M, Tsuda T, et al.CT and MR cgolangiography: advantage and pitfalls in the perioperative evaluation of biliary tree.*British Journal of Radiology*, 2012;85:887-96
10. Pente SG, Bannura GC. Radiological anatomy of the biliary tract: variations and congenital abnormalities. *World Journal of Surgery* 1983; 7:271-6.
11. Morteale. K, Ros P.R, Anatomic variants of the biliary tree: MR cholangiographic findings and clinical applications. *American Journal of Roentgenology*, 2001;177:389-394.

12. Berci G. Biliary ductal anatomy and anomalies: the role of intraoperative cholangiography during laparoscopic cholecystectomy. *Surgical Clinics of North America*, 1992;72:1069-1075
13. Sayed A.T, Ramin N, Sayed E.A, Fardad. E, Gholam R.S, Ahad E, Anatomical Variations of Biliary Tree Found with Endoscopic Retrograde Cholangiopancreatography in a Referral Center in Southern Iran. *Middle East Journal Of Digestive Disease*, October 2017; 9(4).
14. Kaude JV. The width of the common bile duct in relation to age and stone disease. An ultrasonographic study. *Euro Journal of Radiology* 1983; 3: 115-7.
15. Bachar GN, Cohen M, Belenky A, Atar E, Gideon S. et al. Effect of aging on the adult extrahepatic bile duct: a sonographic study. *Jornal of Ultrasound in Medicine*, 2003; 22: 879-82.
16. Daradkeh S, Tarawneh E, AL-Hadidy A. Factors affecting common bile duct diameter. *Hepatogastroenterology*, 2005; 52: 1659-61.
17. Tom C, Ruei-Hung C, ChiaoHung A, MingLii J, ChounChen R. The diameter of the common bile duct in an asymptomatic Taiwanese population: Measurement by magnetic resonance cholangiopancreatography. *Journal of the Chinese Medical Association*, August 2012; 75(8):384-388.
18. Kaim A, Steinke K, Frank M, Enriquez R, Kirsch E, Bongartz G et al. Diameter of the common bile duct in the elderly patient: measurement by ultrasound. *European Radiology*, 1998; 8(8):1413-1415.
19. Niederau C, Muller J, Sonnenberg A, Scholten T, Erckenbrecht J, Fritsch WP, et al. Extrahepatic bile ducts in healthy subjects, in patients with cholelithiasis, and postcholecystectomy patients: a prospective ultrasonic study. *Jornal of Clinical Ultrasound*, 1983; 11(1):23-27.
20. Bowie JD. What is the upper limit of normal for the common bile duct on ultrasound: how much do you want it to be? *American Journal of Gastroenterology*, 2000; 95(4):897-900.
21. Wu CC, Ho YH, Chen CY. Effect of aging on common bile duct diameter: a real-time ultrasonographic study. *Jornal of Clinical Ultrasound*, 1984; 12(8):473-478.
22. Adibi A, Givechian B. Diameter of common bile duct: What are the predicting factors? *Jornal of Research in Medical Sciences*, May&June 2007; Vol 2, No 3. 121-124.
23. Attili AF, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholecystolithiasis (M.I.COL). *American Journal of Epidemiology*, 1995; 141: 158-65
24. Barbara L, et al. A population study on the prevalence of gallstone disease: the Sirmione study. *Hepatology* 1987; 7:913-17
25. Boys JA, Doorly MG, Zehetner J, Dhanireddy KK, Senagore AJ. Can ultrasound common bile duct diameter predict common bile duct Stones in the setting of acute cholecystitis? *American Journal of Surgery*, Mar 2014; 207(3):432-435.
26. Poralla T, Staritz M, Manns M, Klose K, Hommel G, Meyer zum Büschenfelde KH. Age and sex dependency of bile duct diameter and bile duct pressure an ERC manometry study. *Zeitschrift für Gastroenterologie*, 01 May 1985; 23(5):235-239.
27. Matcuk GR Jr, Grant EG, Ralls PW. Ultrasound measurements of the bile ducts and gallbladder: normal ranges and effects of age, sex, cholecystectomy, and pathologic states. *Ultrasound quarterly*, March 2014; 30(1):41-48.

28. Festi D, Dormi A, Capodicasa S, Staniscia T, Attili A, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A., Incidence of gallstone disease in Italy: Results from amulticenter, population-based Italian study (the MICOLproject). *World Journal of Gastroenterology*, 2008 September;14.
29. Palermo M, Berkowski D.E, Córdoba J.P, Verde J.M, Giménez M.E, Prevalence of cholelithiasis in Buenos Aires,Argentina, Department of Gastrointestinal.Surgery. Hospital de Clínicas José de San Martín, University of Buenos Aires, *Argentina.Acta Gastroenterology Latinoam*, 2013;43:98-105.
30. McMichael AJ, Baghurst PA, Scragg RK. A case-control study of smoking and gallbladder disease:importance of examining time relations. *Epidemiology* 1992;3:519-522.
31. Öztürk H, Beyler A.R, Safra kesesi taşlarında epdemioloji ve tedavi, *Güncel Gastroenteroloji*,1997.
32. Yıldırım.B, Aktürk Y, Fırat M.M, Öztürk B, Özüğurlu F, Şahin İ,ve ark. Tokat ili erişkinleri'nde kolelitiazis sıklığı ve olası risk faktörleri, *Akademik Gastroenteroloji Dergisi*, 2008; 7 (2): 83-86).
33. Pancorbo M.C, Carballo F, Horcajo P, Aldeguer M, de la Villa I, Nieto E.Mari'a Gaspar J., de la Morena1 J., Prevalence and Associated Factors for GallstoneDisease: Results of a Population Survey in Spain Department of Internal Medicine and Department of Biochemistry, University General Hospital ofGuadalajara and niversity of Alcalá de Henares, Madrid, Spain.
34. Sezer B. Edirne ilinde Aseptomatik Erişkinlerde Kolelitiazis sıklığı. Uzmanlık tezi. Trakya Üniversitesi Tıp fakültesi İç Hastalıkları A.D.Edirne, 2016.
35. Sun H, Tang H, Jiang S, Zeng L, En-Qiang C, Tao Z, You-Juan W. Gender and metabolic difference of gallstone disease. *World Journal of Gastroenterology*, 2009 April 21;15(15)1886-1891.
36. Youming D, Bin W, Weixing W, Binghua W, Ruoyu L, Bangchang C. The effect of h(1) calponin expression on gallstone formation in pregnancy. *Saudi Medical Journal*, 2006;27:1661-1666.
37. Tierney S, Nakeeb A, Wong O, Lipsett PA, Sostre S, Pitt HA, Lillemoe KD. Progesterone alters biliary flow dynamics. *Annals of Surgery*, 1999; 229: 205-209.
38. Maurer KR, Everhart JE, Knowler WC, Shawker TH, Roth HP. Risk factors for gallstone disease in the Hispanic populations of the United States. *American Journal of Epidemiology*, 1990; 131:836-844.
39. Khan MK, Jalil MA, Khan MS. Oral contraceptives in gallstone diseases. *Mymensingh Medical Journal*, 2007; 16: S40-S45.
40. Maringhini A, Ciambra M, Baccelliere P, Raimondo M, Orlando A, Tine F,Grasso R, Randazzo MA, Barresi L, Gullo D, et al. Biliary sludge and gallstones in pregnancy: incidence, risk factors, and natural history. *Annals of Internal Medicine*. 1993;119(2):116–20.