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The global prevalence of gallstones in pregnancy: A systematic review and meta-analysis

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ABSTRACT

Background: Gallstone disease is the second most common non-gynecological disease that may require surgical intervention during pregnancy. This study investigates the global prevalence of gallstones in pregnancy through a systematic review and meta-analysis.

Methods: A systematic review and meta-analysis of studies that reported the global prevalence of gallstones in pregnancy was conducted. PubMed, Scopus, Web of Science, Embase, ScienceDirect, and Google Scholar were searched for studies published up to September 2022.

Results: In a review of 31 studies with a sample size of 190,714 people, the I^2 heterogeneity test showed high heterogeneity (I^2 = 98.8%). Therefore, the random effects method was used to analyze the results. The prevalence of gallstones was reported as 3.6% (95% CI: 1.9–6.7%). The highest prevalence of gallstones by continent was reported in America, at 6.8% (95% CI: 4.2–10.8%). The Egger test showed no evidence of publication bias (p = 0.609).

Conclusion: Based on the results of this study, health policymakers should emphasize to the target community and the medical staff dealing with pregnant women the importance of screening for gallstones during pregnancy.

Background

Gallstones are classified into pure cholesterol, pigmented or mixed stones based on their main composition [1]. These stones are formed in the gallbladder and biliary tract [2] and can be symptomatic or asymptomatic. Their size can range from grains of sand to golf balls [3] and can be easily detected by ultrasound [4].

Gallbladder diseases have a high prevalence worldwide, with gallstones being the most common type [5] and one of the most common gastrointestinal disorders in the United States. Gallstones are considered a more common disease in developed populations, but they are present worldwide [6]. Women are 1.5–3 times more likely than men to develop gallstones [4].

Most gallstones are formed from cholesterol absorbed from the diet (2), slow evacuation of bile from the gallbladder [7], and biliary obstruction due to various causes, such as narrowing of the bile duct or neoplasm [7]. Other pathogenic factors include excessive secretion of biliary mucin, reduced mobility of the gallbladder, dyslipidemia, insulin resistance [8], use of certain drugs (estrogens, fibrates, somatostatin analogs), gallbladder stasis, and female gender [9], metabolic syndrome, rapid weight loss, Crohn's disease, bowel resection [9], menopause, and pregnancy hormone therapy [4].

Gallstone disease is the second most common non-gynecological disease that may require surgical intervention during pregnancy [4],

Abbreviation: **WoS**, Web of Science.

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affecting up to 12% of pregnant women [10]. Pregnancy can increase the risk of gallstone formation due to the formation of new biliary sludge and gallstones [4], numerous physiological and hormonal changes that occur to support the growth of the fetus [11], and an increase in progesterone that reduces the contraction of the gallbladder, which leads to stasis. Estrogen also causes an increase in cholesterol in the bile and decreases the gallbladder's contraction, which means that women of reproductive age or women who use contraceptives containing estrogen have a double risk of gallstone formation compared to men [1]. BMI is also a determining factor for gallstone disease in pregnancy and early postpartum [12].

Some severe gallstone operations may require cholecystectomy [3]. Cholecystectomy and laparoscopy can be performed in every trimester of pregnancy if indicated immediately [12,13]. A pregnant woman who shows symptoms of acute cholecystitis in the first trimester has a significant risk of recurrence and should undergo early elective surgery [13,14].

Given the numerous complications of gallstones, the importance of pregnancy, and the health of the mother and fetus, we conducted a systematic review and meta-analysis of the global prevalence of gallstones in pregnancy. This study aimed to provide important evidence to draw attention to the issue of this disease in pregnant mothers worldwide.

Method

We conducted our initial search in August 2022. This systematic review used PubMed, Web of Science, Google Scholar, Scopus, ScienceDirect, and Embase databases to identify relevant studies using the keywords "prevalence", "outbreak", "burden", "gallstone", "cholelithiasis", "pregnancy" "gravidity", "conception", and "gestation". To ensure the comprehensiveness of the search, no restrictions were placed on the year of publication of the articles, and the identified information was transferred to the information management software (EndNote). In order to maximize the number of relevant studies, the reference lists of the identified relevant articles were manually reviewed. Searches were last updated in September 2022.

Inclusion and exclusion criteria

The study inclusion criteria were that the studies: (1) reported the global prevalence of gallstones in pregnancy; (2) had their full text available; (3) provided sufficient data on sample size and prevalence; and (4)- were written in English. The study exclusion criteria were that the studies: (1) were not case reports or case series studies; (2) were review studies; (3) were duplicates of other studies; (4) had insufficient data on prevalence or sample size); (5) were not written in English; or (6) did not accurately report the number of pregnant women.

Study selection

Study selection was performed in accordance with the PRISMA guidelines. Duplicate studies in different databases were excluded. The titles and abstracts of the studies were screened, and irrelevant studies were excluded based on the inclusion and exclusion criteria. The full texts of the remaining studies were then evaluated, and any studies that did not meet the inclusion criteria were removed. Two researchers independently reviewed all sources and extracted data to avoid bias.

Quality evaluation

In order to validate and evaluate the quality of articles, a checklist was used according to observational studies. The Strengthening the Reporting of Observational Studies in Epidemiology checklist (STROBE) consists of six sections: title, abstract, introduction, methods, results, and discussion. In total, this checklist consists of 32 items. Articles with a score of 16 and above were considered good and moderate methodological quality.

Table 1
Summary of characteristics of included studies of the prevalence of gallstones in pregnancy- Sonographic findings.

Author	Year	Reign	Age	Sample size of pregnant	Prevalence of Gallstone in pregnant
Stauffer et al. [16]	1982	USA	20–40	338	3.5%
Buiumsohn et al.[17]	1984	Italy	20–34	36	5.6%
Williamson et al.[18]	1984	USA	19–40	142	11.3%
Mintz et al. [19]	1985	USA	-	103	3.9%
Christenson [20]	1986	USA	-	175	6.3%
Maringhini et al.[21]	1987	USA	26.8 ± 5.7	298	5.2%
Sali et al.[22]	1989	Australia	16–42	121	4.1%
Basso et al. [23]	1992	Ireland	15–43	512	4.5%
Valdivieso et al.[24]	1993	Chile	16–30	980	12.2%
Maringhini et al.[25]	1993	Italy	27.0 ± 5.0	272	2%
Giangrande et al.[26]	1993	Italy	-	56	2.9%
Tsimoyiannis et al.[27]	1994	Greece	25 ± 3	669	2%
Deutchman et al.[28]	1994	USA	13–40	228	5.3%
Hansen et al. [29]	1994	USA	15–42	585	5.3%
Ferguson et al. [30]	1994	USA	-	572	4.2%
De Alba et al. [31]	1997	Mexico	-	292	14.04%
Bodegraven et al.[32]	1998	Netherlands	29.1 ± 4.1	111	5.4%
Akute et al. [33]	1999	Nigeria	15–54	3832	2.1%
Rambal et al. [34]	2001	India	16–40	200	6%
Hossain et al. [35]	2003	Bangladesh	20–45	1336	8.08%
Lindseth et al. [36]	2004	USA	18–40	128	12.5%
Ko et al.[37]	2005	USA	-	3254	1.8%
Bolukbas et al. [38]	2006	Turkey	19–35	97	6.3%
Tica et al.[39]	2010	Romania	Md: 25.11	130	9.23%
Moghaddam et al.[40]	2013	Iran	26.3 ± 5.0	380	0.7%
Ibitoye et al. [41]	2014	Nigeria	14–43	1283	2.9%
Ilhan et al.[42]	2016	Nigeria	28.0 ± 5.0	96,567	0.06%
Kolbeinsson et al.[43]	2016	Iceland	Mn: 29	77,000	0.09%
Ramirez et al. [44]	2016	Mexico	15–35	348	16%
Idowu et al. [45]	2019	Nigeria	18–44	656	1.7%
Nimanya et al. [46]	2020	Uganda	-	13	3%

Statistical analysis

The results extracted from this study were entered into the Comprehensive Meta-Analysis software (Version 2). Heterogeneity among the studies was assessed through the I^2 test. To examine publication bias, the Egger test was used at a significance level of 0.05, as well

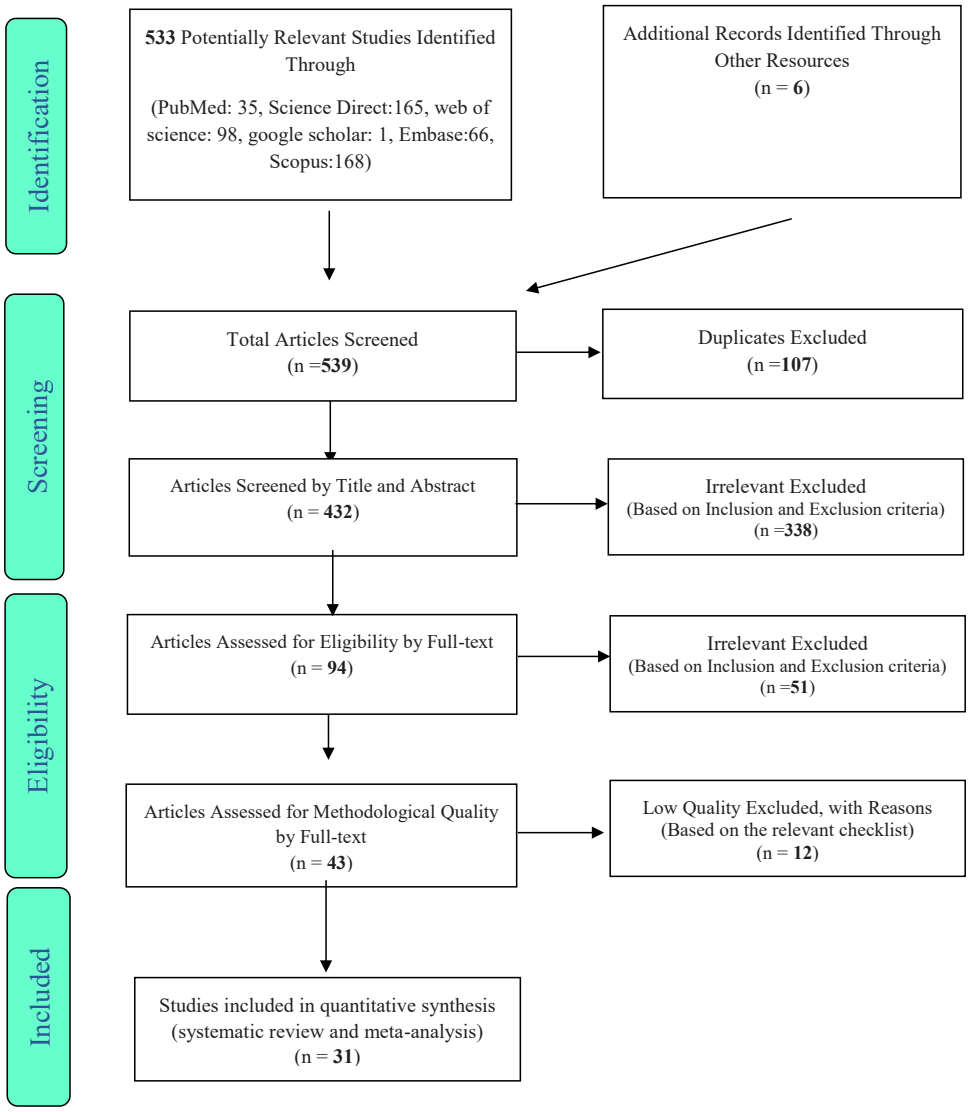


Fig. 1. The flowchart on the stages of including the studies in the systematic review and meta-analysis (PRISMA 2009(.

as the Funnel plot.

Results

In this systematic review and meta-analysis, the study data revealed the global prevalence of gallstones in pregnancy, assessed in accordance with the PRISMA guidelines. A comprehensive search across databases yielded 533 articles, with an additional six potentially relevant articles identified through manual search and subsequently transferred to the information management software (Endnote). Following the removal of 107 articles due to duplication, a screening phase involved the evaluation of titles and abstracts, leading to the exclusion of 338 articles based on predefined inclusion and exclusion criteria. During the merit evaluation stage, 51 articles were excluded based on full-text assessment and inclusion and exclusion criteria. Further qualitative evaluation eliminated studies with poor methodological quality based on the score obtained from the STROBE checklist. Finally, 31 studies were included in the final evaluation. The information on these 31 studies is reported in Table 1 and Fig. 1.

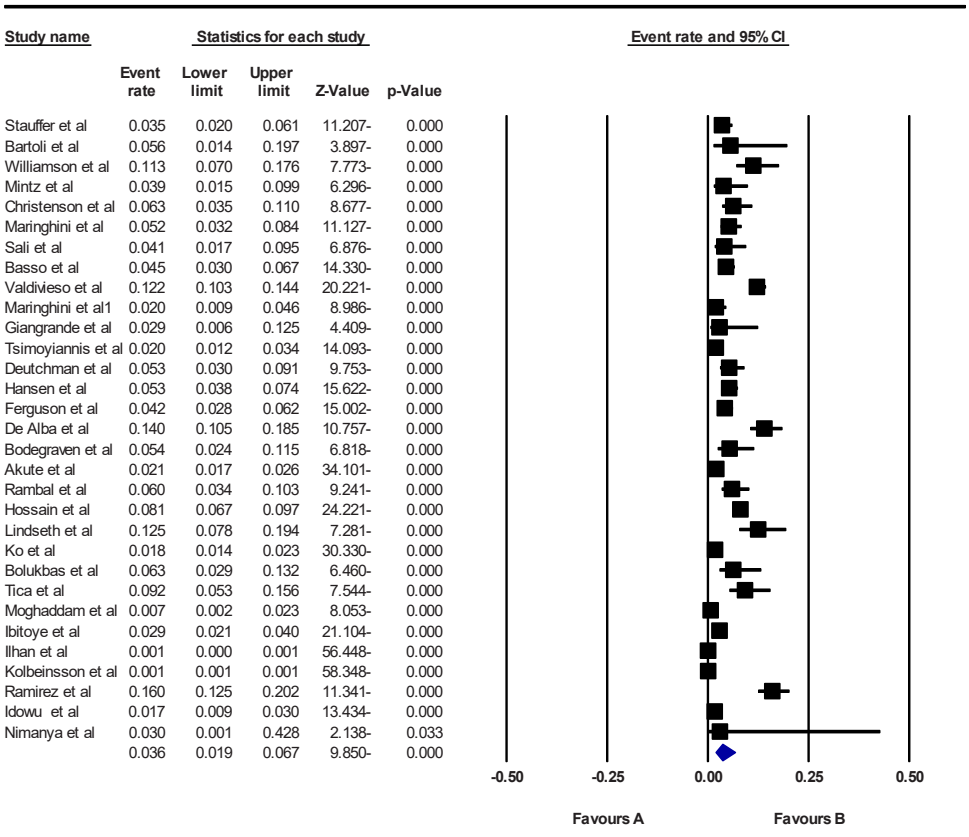
All the included studies were of observational nature, predominantly conducted in North America continent but encompassing diverse geographical locations. In addition, all studies used ultrasound tools to diagnose gallstones in pregnant patients.

Among the studies included in Table 1, a study by Ramirez et al. in 2016 conducted in Mexico reported the highest prevalence of gallstones (16%) among pregnant women aged 15–35 years (14). In contrast, Ihan et al. in 2016 reported the lowest prevalence of gallstones (0.06%) in pregnant women with an average age of 28.0 ± 5.0 in Nigeria [15].

In the review of 31 studies with a sample size of 190,714 individuals, the I^2 heterogeneity test showed high heterogeneity (I^2: 98.8%). Consequently, the random effects model was used to analyze the results. According to the meta-analysis results, the prevalence of gallstones was determined to be 3.6 (95% CI: 1.9–6.7) (Fig. 2). The assessment of publication bias in the studies using the Egger test indicated the absence of such bias within the studies ($p = 0.609$) (Fig. 3).

In examining the factors affecting the heterogeneity of studies and investigating the effect of sample size on this heterogeneity, it was reported that an increase in sample size corresponded to a decrease in the prevalence of gallstones ($p < 0.05$) (Fig. 4). Moreover, in the context of recent studies, a comparison with older studies revealed a decrease in the prevalence of gallstones ($p < 0.05$) (Fig. 5).

Based on the results presented in Table 2, which reports the subgroup analysis of the prevalence of gallstones by continent, the highest prevalence was reported in the Americas with a prevalence of 6.8 (95% CI: 4.2–10.8) (Table 2).



Meta Analysis

Fig. 2. Forest plot of gallstone prevalence based on random effects method.

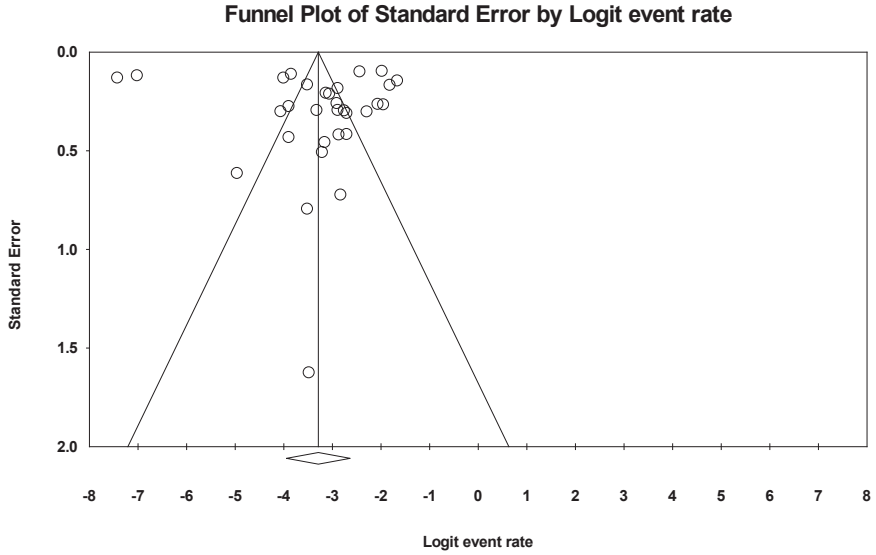


Fig. 3. Funnel plot of the publication bias in the reviewed studies.

Discussion

The present study is the first systematic review and meta-analysis of the global prevalence of gallstones in pregnancy. To our knowledge, no systematic review has previously investigated the global prevalence of gallstones in pregnancy. This study was compiled using the most optimal secondary analysis methods among 31 qualified primary studies. All the studies used were observational.

The most common risk factors for gallstones are obesity, diabetes, hormones such as estrogen, pregnancy, hemolytic disease, and cirrhosis; The disease often manifests itself as pain in the epigastrium and upper right side of the abdomen 30–60 min after eating [47]. Ultrasound is the

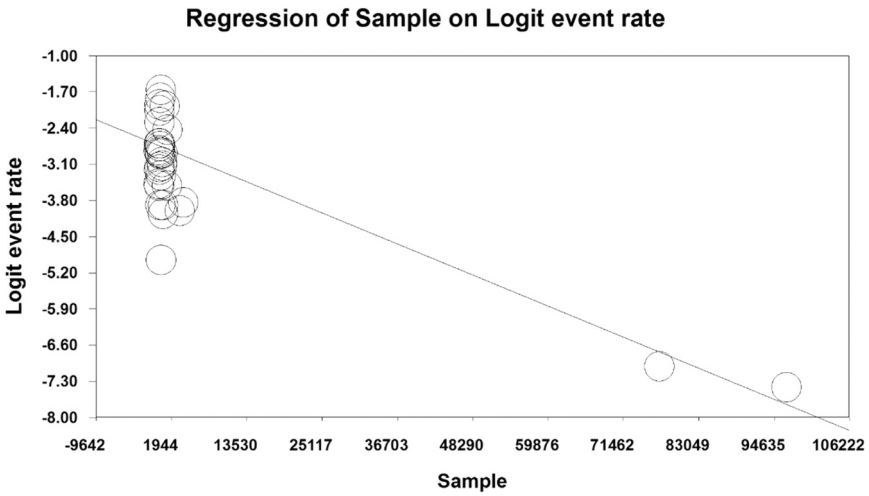


Fig. 4. Meta-regression of the effect of sample size based on the name of gallstones.

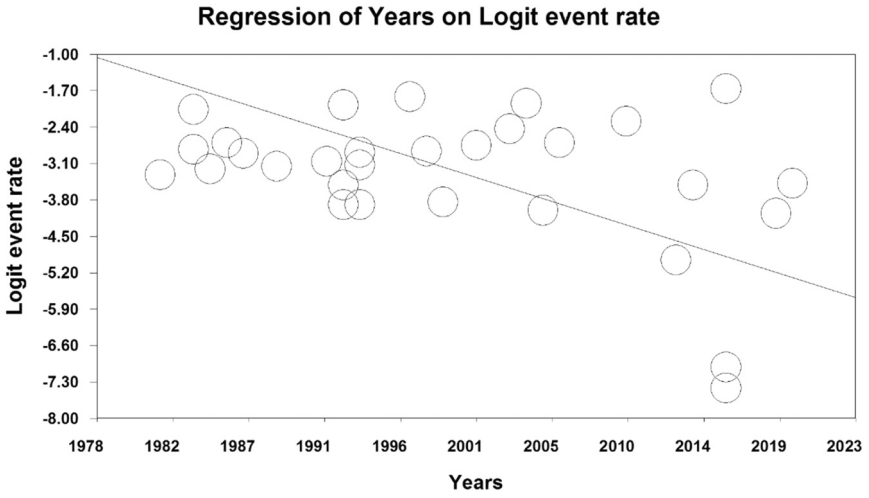


Fig. 5. Meta-regression of the effect of the year of studies on the prevalence of gallstones.

Table 2
Subgroup analysis of gallstone prevalence by continent.

Continent	N	Sample size	I^2	Prevalence
America	12	7145	95.4	6.8 (95%CI: 4.2–10.8)
Europe	9	79,084	98.5	2.7 (95%CI: 0.6–11.4)
Asia	4	2013	82.5	4.7 (95%CI: 2.3–9.7)
Africa	5	102,351	99.2	1.1 (95%CI: 0.2–6.6)

preferred imaging method in pregnant women because it is quick, inexpensive, sensitive, and does not use ionizing radiation [48]. Treatment for gallstones depends on the severity of the patient's symptoms [49,50].

The female gender is one of the main risk factors for gallstone disease, and the commonly held belief that women are at greater risk for developing gallstones than men can largely be attributed to external risk factors such as pregnancy and sex hormones. Among these factors, the number of pregnancies is the main reason for the high rate of gallstone disease in women. Also, sex hormones are most likely responsible for increasing the risk of contracting this disease. For instance, estrogen has been linked to increased secretion of bile cholesterol, leading to excessive cholesterol saturation within bile [51,52]. In a study of 210 patients under the age of 30, with an average age of 25 $\pm$ 3 years, and where the majority of the population were women (170 individuals), an exploration of the risk factors revealed that 31.84% of female patients had used oral contraceptives. Furthermore, at the time of referral, 20.48% were pregnant, and 27.14% had a history of gallstones. In addition, it was found that 114 people were overweight, while 108 (51.43%) had elevated triglyceride and 115 (54.76%) had high cholesterol levels. The results showed that young people are susceptible to symptomatic gallstones, and the rate of this disease was significantly higher in women, in patients with high cholesterol and triglyceride levels and abnormal body mass index (BMI) [3].

Constantinescu et al., in a study on patients aged 16–25 years, identified several significant risk factors for the development of gallstones in this age group, including obesity, pregnancy, age, and female gender [47]. Similarly, other studies have highlighted pregnancy and breastfeeding as risk factors associated with gallstones [53,54].

In a cohort study that included only pregnant women, BMI has been identified as a determining factor for gallstone disease during pregnancy and the early postpartum period [12]. Tika et al. also reported a higher prevalence of biliary disorders among older multiparous pregnant women in their third trimester [39]. Ramirez et al. reported a gallstone prevalence of 16% among 348 pregnant women.

In one study, there was one (9.1%) primiparous woman with gallstones, while 10 (90.9%) women with gallstones had a history of two or more pregnancies. These findings showed that the incidence of gallstones increases with the number of pregnancies [45], and previous

studies also confirmed this [27,35]. Another study also showed that the more pregnant a woman is, the more likely she will not only get pregnant with gallstones but also get them during pregnancy. Frequent changes in the gallbladder volume during each pregnancy, coupled with the gallbladder's residual volume and the bile's cholesterol content, may lead to conditions that contribute to the formation of gallstones [27]. However, another study showed that age, female gender, BMI, and positive family history are risk factors for developing gallstones. However, pregnancy and the number of pregnancies are not risk factors for gallstone disease [55]. Similarly, a review by Wattemberg et al. reported an absence of the relationship between pregnancy and gallstone disease [10].

Giangrande et al., in their investigation involving ultrasound examinations of 56 women during the first trimester (where one woman had gallstones and four exhibited biliary sludge) and 49 women during the third trimester (with two women with gallstones and seven showing biliary sludge), observed a higher prevalence of gallstone disease in pregnant women compared to biliary sludge disease [27].

One of the limitations of this meta-analysis is that the information related to the weight of pregnant mothers and the genes or family history of gallbladder disease was not examined in some studies. These may play a role in the pathogenesis of gallstone formation. Another limitation was the uneven distribution of studies among different countries. Additionally, a larger sample size could have provided more insight into the factors contributing to gallstone formation among pregnant women. The included studies were limited to only those published in English, meaning studies with other languages may have been overlooked. On the other hand, this study was limited to the population of pregnant women; therefore, it is recommended to measure the prevalence of this disease in other populations as well.

Strengths and limitations

One of the most important strengths of this study is the comprehensive review of all databases and access to a large number of articles with very high sample size. Additionally, categorising data based on continents increases the study's credibility. However, a significant limitation of the current study is the lack of interventional studies due to the nature of these studies, which may not have been possible to include population studies.

Recommendation

It is recommended that future review studies based on observational and interventional studies be focused so that interventional measures in this field can also be investigated.

Conclusion

Based on the results of the present study, considering the health of the mother and fetus during pregnancy is of particular importance, health policymakers can use the results of the current meta-analysis to emphasize the importance of screening for this disease before and during pregnancy as a research priority.

Ethics approval and consent to participate

Ethics approval was received from the ethics committee of deputy of research and technology, Kermanshah University of Medical Sciences (IR.KUMS.REC.1401.395).

Consent for publication

Not applicable.

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CRediT authorship contribution statement

NS and, RH and MM contributed to the design, MM conducted the statistical analysis. MM and RH, and PH prepared the manuscript. AAK and AHA and SHSH, and MM assisted in designing the study and helped in the interpretation of the study. All authors have read and approved the content of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data Availability

Datasets are available through the corresponding author upon reasonable request.

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