Oral Contraceptives and the Risk of Gallbladder Disease: A Meta-Analysis

ABSTRACT

Objectives. This study was designed to assess the risk of gallbladder disease due to oral contraceptive use by conducting a thorough literature review.

Methods. Controlled epidemiologic studies published through March 1992 were systematically searched and evaluated. Of 25 studies (27 publications), 9 could stand the test of critical appraisal with respect to validity. Restriction to these studies was judged to circumvent publication bias at the same time.

Results. Oral contraceptive use is associated with a slightly and transiently increased rate of gallbladder disease. The results of six selected studies in which asymptomatic women were screened for gallstones were strikingly similar. Pooling of these results yielded an odds ratio, for ever vs never oral contraceptive use, of 1.36. A dose–effect relationship was indicated, suggesting that modern low-dose oral contraceptives are safer than older formulas, but an effect cannot be excluded.

Conclusions. Considering the large efforts already devoted to this exposure–disease relationship, the probably weak effect, and the rapidly changing formulas of oral contraceptives, the authors suggest that the safety of new oral contraceptives be evaluated by studying bile saturation and biliary function rather than by waiting for gallbladder disease to develop. (*Am J Public Health.* 1993;83: 1113–1120)

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Introduction

Epidemiologic studies in the 1970s indicated that an increased risk of gallbladder disease was associated with oral contraceptive use.[1–7] Later research, however, yielded conflicting results.[8–27] This inconsistency raised several questions, which are addressed in this review:

1. Were the older studies systematically biased by flaws in their design (or are the newer studies less valid)?
2. Was there a tendency at the time of the earlier studies to find only "positive" studies interesting enough for publication?
3. How should the evidence in the studies be weighted?
4. Are there explanations for the inconsistencies? For example, is the effect absent in later studies because modern low-dose oral contraceptives lack an effect on gallbladder disease?

Because oral contraceptives are widely used, even a small effect of oral contraceptive use on the occurrence of gallbladder disease may have a considerable impact on public health. Therefore, we undertook a systematic review of controlled epidemiological studies on this subject.

Methods

Original publications were searched in MEDLINE (1983 to 1992-III) and EXCERPTA MEDICA (1983 to 1991-XII). Earlier publications were found via references in later publications and review articles.[28–32] The review was restricted to controlled epidemiologic studies of gallbladder disease (except gallbladder cancer). The studies were compared with respect to their main findings (the results over all subgroups together). They were rated on validity, focusing on particular problems associated with oral contraceptive use and gallbladder disease (discussed below).

When confidence limits were lacking in the original publication, they were computed from the raw data or from statistical parameters presented; unless stated otherwise, the test-based method[33] was used. Pooling of odds ratios from selected studies was performed by weighting the natural logarithms of the odds ratios with the inverse of their variances,[34] the latter computed from standard errors of logistic regression or estimated from confidence intervals or chi-squares. Publication bias was evaluated in a funnel plot, plotting the point estimates against their standard errors[35] (after taking the natural log to derive a normal distribution).

Effects in subgroups were considered only in the light of specific hypotheses.

Results

We found a total of 27 publications, concerning 25 studies. Four studies were follow-up studies (Table 1). After the initial publication of two large cohort studies, the results of extended follow-up appeared some years later (the Royal College of General Practitioners Oral Contraceptives Study [Royal-I and -II][2,12] and the Oxford/Family Planning Association Contraceptives Study [Oxford-I and -II][5,13]). Nine studies were case-control studies with new cases of gallstone disease (Table

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Editor's Note. See related articles in this issue's Policy Forum.

TABLE 1—Follow-Up Studies on Oral Contraceptive (OC) Use and Gallbladder Disease

Author	Year	Subjects at Admission; Duration of Follow-Up Diagnosis (No. Cases) OC use	Validity Ratings[a] Confounding	Contraindication	Detection	Registration	Publication	Rate Ratio[b]	95% CI
*Royal-I[2]	1974	OC users and never users; 4 y Self-reported gallbladder disease (201) OC use current/never	+	+	+	+	+	1.3	1.0, 1.8
*Oxford-I (Vessey[5])	1976	Family planning clinic attendants using OCs, diaphragm, or IUD; 1–4 y Clinical gallbladder disease (96) OC use, diaphragm, IUD	+	+	+	+	+	1.6	0.9, 2.7[c]
Ramcharan et al.[11]	1981	Subscribers to health insurance; 5–9 y Clinical gallbladder disease (304) OC use current/never	+	0	–	+	+	0.8	0.6, 1.3[d]
*Royal-II[12]	1982	OC users and never users; 10 y Self-reported gallbladder disease (768) OC use current/nonuse	+	0	0	+	+	1.1	1.0, 1.3
*Oxford-II (Layde et al.[13])	1982	Family planning clinic attendants using OCs, diaphragm, or IUD; 7–13 y Clinical gallbladder disease (227) OC use ever/never	+	0	+	+	+	1.3	0.9, 1.7[e]
Sichieri et al.[25]	1990	General population, premenopausal; about 10 y Clinical gallstone disease (111) OC use in last 6 mo yes/no	–	0	–	+	+	1.2	0.8, 1.8

[a]+ denotes adequate and – denotes inadequate management of bias; 0 denotes bias not likely.
[b]All studies had a person-time type of analysis.
[c]Diaphragm and IUD combined; OC vs diaphragm rate ratio (RR) = 1.5, OC vs IUD RR = 1.7, χ^2 (2 *df*) = 4.5; the corresponding 1 *df* chi-square value was used for the test-based 95% CI of the combined RR.
[d]Result for current OC use; the RR for past OC use was 1.1 (0.8, 1.4).
[e]Chi-square for the test-based 95% CI was computed from the *P* value presented (*P* = .13).

2). One publication reported two case-control studies with the same case series[15]; these are included as separate studies (A and B) in Table 2. In nine studies healthy women were screened for gallstones by ultrasound or x-ray (screening studies, Table 3). The remaining four studies related prevalent cases of gallbladder disease to oral contraceptive use[8,10,18] or related gallbladder disease and oral contraceptive use reported at any time during a 2-year study period[19] (Table 4).

The main findings are shown in the last columns of the tables. The results vary considerably (rate ratios or odds ratios range from 0.3 to 6.0). Rate ratios or odds ratios of 2.0 or higher were observed only in studies reported up to 1982 (5 of 14 studies; 4 were statistically significant); thereafter no rate ratio or odds ratio higher than 1.4 was observed. The Royal study and the Oxford study both showed a decrease of the effect at extended follow-up (rate ratio decreased from 1.3 to 1.1 and from 1.6 to 1.3, respectively; Table 1).[2,5,12,13]

Internal Validity of the Studies

The next section documents our ratings of the validity of the studies: adequate (+) or inadequate (–) management of bias, or bias not likely (0) (see Tables 1 through 4).

Confounding by pregnancy. Among the possible confounders of the association between oral contraceptive use and gallbladder disease, pregnancy deserves special attention. Women who use oral contraceptives most likely will not get pregnant, whereas nonusers may; pregnancy itself increases the risk of gallbladder disease. The design that best safeguards against confounding by pregnancy was encountered in the Oxford study (Table 1). This study compared the rates of gallbladder disease associated with the use of oral contraceptives, intrauterine devices, and pessaries.[5] It was hoped that this procedure made the groups comparable with respect to the occurrence of pregnancies. Remaining differences were controlled for in the analysis. An example of a study that did not pay attention to confounding by pregnancies was a small case-control study by Honoré[7] of women aged 14 to 20 years; the study yielded a relative risk of 2.5 (Table 3). Possibly, women who had been pregnant at such a young age used oral contraceptives thereafter, whereas women who were not yet very sexually active neither used oral contraceptives nor got pregnant. If so, the results for oral contraceptive use may largely be due to confounding by pregnancy, since the effect of pregnancy was of sufficient strength to cause confounding. The tables indicate which studies paid attention to confounding by pregnancy (or parity) at all (rated + if yes, – if not).

Confounding by contraindication. Women with a known high risk of gallbladder disease (e.g., positive family history, gross obesity) may tend to choose other ways of contraception to avoid a further increase of the risk by oral contraceptive use. As a result, oral contraceptive users would be women with a relatively low risk of gallbladder disease, compared with nonusers. Studies ignoring this fact would underestimate the effect of oral contraceptive use or even suggest a protective effect. However, gallbladder disease as an adverse effect of oral contraceptive use has always been overshadowed by other adverse effects of oral contraceptive use, like thromboembolic disease. Therefore, we think that con-

TABLE 2—Case–Control Studies on Oral Contraceptive (OC) Use and Incidence of Gallstones Found by Screening

Author	Year	Case Patients (No.); Control Patients (No.); Age Type of Analysis; OC Use	Validity Ratings[a]					Odds Ratio	95% CI
			Confounding	Contraindication	Detection	Registration	Publication		
Boston[1]	1973	Clinical gallstone disease (212); acute illness or elective surgery (842); 20–34 y Standardized, OC use ever/never	–	+	+	+	–	2.0	1.4, 2.8
Stolley et al.[3]	1975	Biliary tract surgery (85); hospital (1217); 15–49 y Crude; OC use in past 2 y yes/no	–	+	+	+	–	2.0	1.2, 3.2
Howat et al.[4]	1975	Surgery for gallstone disease (50); minor surgery or trauma (50); 20–45 y Crude; OC use > 6 mo yes/no	+[b]	0	–	–	–	6.0	2.6, 14
Ahlberg[6]	1979	Positive cholecystogram (42); minor surgery (56); ≤30 y Crude; OC use > 6 mo yes/no	+	0	–	–	+	. . .[c]	. . .[c]
Honorè[7]	1980	Surgery for gallstone disease (31); surgery for tonsillitis or nasal septum deviation (112); 14–20 y Mantel-Haenszel; OC use ever/never	–	0	–	–	–	2.5	0.8, 7.1
Sastic & Glassman[14]	1982	Surgery for gallstone disease (96); surgery for appendicitis (96); ≤25 y Mantel-Haenszel[d]; OC use ever/never	–	0	–	–	–	2.5	1.1, 6.2
*Scragg et al. (A)[15]	1984	Clinical gallstone disease (200); hospital (234); <29 to >60 y Mantel-Haenszel; OC use ever/never	+	0	+	+[e]	+	0.7	0.5, 1.0
Scragg et al. (B)[15]	1984	Clinical gallstone disease (200); general population (182); <29 to >60 y Mantel-Haenszel; OC use ever/never	+[f]	0	–	–	+	0.5	0.3, 0.9
van Beek et al.[27]	1991	Surgery for gallstone disease (53); surgery for appendicitis (53); <30 y Crude; OC use ever/never	–	0	–	–	+	. . .[g]	. . .[g]

[a] + denotes adequate and – denotes inadequate management of bias; 0 denotes bias not likely.
[b] Matched on parity, but no matched analysis; odds ratio may be underestimated.
[c] No data presented. The authors stated that among nonparous women OC use was more prevalent in case patients than in control patients ($P < .05$), and that this was not true of those who had been pregnant.
[d] Mantel-Haenszel odds ratio (with Cornfield's 95% confidence intervals) from stratified tables that could be reconstituted from the tables presented, controlling for obesity and parity.
[e] Case patients were interviewed before the diagnostic examination; control patients were held ignorant of the hypothesis during the interview.
[f] The authors reported that logistic regression analysis indicated no confounding by parity.
[g] No data presented. The authors stated that no difference could be shown between case and control patients (age-matched case-controls, but no matched analysis).

founding by contraindication cannot lead to severe underestimation of the effect (rated 0).

Biased detection of gallbladder disease. Biased detection occurs when suspicion of gallbladder disease as a side effect tends to enhance the detection of gallstones in oral contraceptive users with vague abdominal complaints. Gallstones are so common[36] that cholecystography or ultrasound of the gallbladder will show gallstones in a considerable proportion of women, even when their complaints are unrelated to gallstones. In the screening studies, no detection bias can occur (rated +). The case-control study by Scragg et al. (A) included a control group of patients who were referred for a radiodiagnostic exam of the gallbladder.[15] In this way selective referral of the cases is balanced by equally selective referral of the controls (rated +).

The decreasing effect found at extended follow-up in the Royal study[12] and the Oxford study[13] cannot be explained by detection bias, because such a bias can but lead to overestimation (rated +). An additional reason why detection bias is not probable in the Royal study is its finding at extended follow-up of an effect of oral contraceptives on cholecystitis only, not on gallstone disease.[12] Detection bias will not be likely to occur if a disease is so severe that it always comes to medical attention, as acute cholecystitis does.

All other studies may be affected by detection bias (rated –) except for four. These four studies were conducted at a time when oral contraceptive use was not suspected as a risk factor for gallbladder disease, as evidenced by the statements of the studies' objectives in the publications.[1–3,5] Therefore, confounding by indication and detection bias could not have occurred in these four studies (rated +).

Biased registration of oral contraceptive use. Another bias occurs when the suspicion of an adverse effect leads to better registration of oral contraceptive use in women with known gallbladder disease than in women with other conditions. Notorious are case-control studies in which information on oral contraceptive use is extracted from the hospital records without oral contraceptive use being recorded systematically. Doctors may particularly notice oral contraceptive use in patients with gallbladder disease and record it. By contrast, they may ignore oral contraceptive use in patients with unrelated dis-

TABLE 3—Screening Studies on Oral Contraceptive (OC) Use and Gallstones Found by Screening with Ultrasound or Oral Cholecystography

Author	Year	Population Screened; Age Diagnosis (No. Cases) Type of Analysis; OC Use	Validity Ratings[a]					Odds Ratio	95% CI
			Confounding	Contraindication	Detection	Registration	Publication		
Williams & Johnston[9]	1980	General population; 15–50 y Gallstones and cholecystectomy (20) Percentage OC users; OC use ever/never[b]	–	0	+	+	+	1.0	0.3, 3.2
*GREPCO[16]	1984	Civil servants; 20–49 y Gallstones and cholecystectomy (38) Logistic regression; OC use ever/never	+	0	+	+	+	1.3	0.8, 2.3
Pixley et al.[17]	1985	Sample from general practice; 40–96 y Gallstones and cholecystectomy (156) Mantel-Haenszel; no details on OC use	?	0	+	+	+	...[c]	...[c]
*Šorf et al.[20]	1987	Healthy young women; mean age 28 y Gallstones, cholecystectomy excluded (26) Raw data[e]; OC use ever/never	+[d]	0	+	+	+	1.3	0.6, 2.9
*Maringhini et al.[21]	1987	Postpartum in hospital; mean age 29 y Gallstones, cholecystectomy and sludge excluded (16) Logistic regression; OC use >6 mo yes/no	+	0	+	+	+	1.4	1.0, 1.8
Barbara et al.[22]	1987	General population; 18–65 y Gallstones and cholecystectomy (132) Mantel-Haenszel; OC use ever/never	?	0	+	+	+	0.7	0.5, 1.3
*Jørgensen[23]	1988	General population; 30, 40, 50, and 60 y Gallstones and cholecystectomy (202) Logistic regression; OC use ever/never	+	0	+	+	+	1.4	1.0, 2.0
*Maurer et al.[24]	1990	General population, 20–74 y Gallstones and cholecystectomy (253) Logistic regression; OC use ever/never	+	0	+	+	+	1.4	1.0, 2.0[f]
*Pannwitz et al.[26]	1990	General population, 12–24 y Gallstones and cholecystectomy (43) Stratified data[g]; OC use ever/never	+	0	+	+	+	1.4	0.5, 4.1
Pooled (only studies indicated by *)								1.36	1.15, 1.62

[a]+ denotes adequate and – denotes inadequate management of bias; 0 denotes bias not likely.
[b]The data presented allowed computation of crude odds ratio and chi-square.
[c]The publication stated that there was no relation between OC use and gallstone disease, but no data were presented.
[d]The study was restricted to parous women.
[e]Crude odds ratio and chi-square computed from 2 × 2 table, combining categories of duration of OC use (no trend with duration observed).
[f]Odds ratio for gallstones found at screening = 1.2 (0.7, 1.8), for status post cholecystectomy = 1.8 (1.1, 2.8).
[g]Mantel-Haenszel odds ratio computed from a stratified table presented in the original paper, controlling for family history, pregnancy (ever/never), and body mass index.

eases. If the latter are selected as a control group, a spurious relation between oral contraceptive use and gallbladder disease will result. We found at least two examples (Table 2): case-control studies that contrasted information from the hospital records of cholecystectomy patients and patients operated on for tonsillitis or nasal septum deviation (Honoré[7]), or appendicitis (Sastic and Glassman[14], van Beek et al.[27]). The publication of Howat's case-control study[4] suggests a similar problem; it states only that information on oral contraceptive use from cholecystectomy patients was contrasted with that from patients who had visited the hospital for surgery or minor trauma. These three studies showed the largest relative risks encountered (2.5, 2.5, and 6.0, respectively).

Such bias is precluded in the following situations (rated +): oral contraceptive use is recorded before the disease occurs (follow-up studies, Table 1), or the interview on oral contraceptive use is performed before the diagnostic examination in asymptomatic people (screening studies, Table 3) or in patients with similar symptoms (case-control study by Scragg et al.[15] of patients who were referred for a radiodiagnostic exam of the gallbladder, designated Scragg et al (A) in Table 2). In the study by Strom et al.[19] (Table 4), the reporting of oral contraceptive use and the reporting of gallbladder disease (to the health insurance company) were independent of one another (rated +). The remaining studies may have been affected by registration bias (rated –), except those performed at a time when suspicion of oral contraceptives had not yet been raised.

Publication Bias

When a large database is screened for all possible relationships, of which only the statistically significant ones are reported, many of the reported relationships are positive by chance. The first publication came from the Boston Collaborative Drug Surveillance Programme,[1] which had been criticized earlier for relating a gamut of diseases to a mass of drugs[37] (Boston, Table 1). Likewise, publication bias may occur when many secondary analyses are performed on data collected for other purposes and only positive ones are published. The case-control study by Stolley et al.[3] (Table 2) was recognizable as re-

TABLE 4—Other Studies on Oral Contraceptive (OC) Use and Gallbladder Disease, with Uncertain Time Relation

Author	Year	Study Design; Age of Subjects Diagnosis (No. Cases) Type of Analysis; OC use	Validity Ratings[a] Confounding	Countraindication	Detection	Registration	Publication	Odds Ratio	95% CI
Diehl et al.[8]	1980	Review of medical records of family health center population; 15–59 y Clinical gallstone disease ever (107) Log-linear regression; OC use ever/never	–	0	–	–	+	. . .[b]	. . .[b]
Pettiti et al.[10]	1981	Health examination of volunteers; age? Self-reported gallbladder disease ever (65) Logistic regression; OC use yes/no	–	0	–	–	+	0.7	0.4, 1.2
Wysowski et al.[18]	1986	Secondary analysis of a study on gallbladder and breast cancer; ?–75 y Self-reported gallbladder disease ever (133) Logistic regression; OC use ever/never	+	0	–	–	+	0.3	0.1, 1.1
Strom et al.[19]	1986	Historical cohort study with medical billing data; 15–44 y Clinical gallbladder disease during the 2-y study period (12 292) Logistic regression; OC use during the 2-y study period yes/no	+[c]	0	–	+	–	1.1	1.1, 1.2

[a]+ denotes adequate and – denotes inadequate management of bias; 0 denotes bias not likely.
[b]The publication stated that there was no relation between OC use and gallstone disease, but no data were presented.
[c]Only controlling for pregnancies that had occurred during the 2-year study period.

sulting from such a secondary analysis. The study by Strom et al.[19] (Table 4) explored the possibility of monitoring adverse drug reactions with medical insurance data. According to the authors, some established relationships were chosen to test this possibility, and the relationship between oral contraceptive use and gallbladder disease was one of the first.[19]

Publication bias may also exist if many "quick and dirty" studies with a low power are undertaken to confirm an adverse drug reaction and only the "positive" ones are published. Two small case-control studies by Howat et al.[4] and Sastic and Glassman[14] were recognizable as such. A small case-control study by Honoré reporting a nonsignificant association between gallstone disease and oral contraceptive use may have been saved from oblivion because it also reported an extremely strong association among parity, obesity, and gallstone disease. Only one small "quick and dirty" case-control study with negative results was found.[27]

The six studies that might have emerged from selective publication (rated – in the tables) appeared to comprise all studies with a rate ratio or odds ratio of 2.0 or more.

Publication bias does not occur in large-scale studies of effects of oral contraceptive use, in which all relationships studied are reported. We identified three such studies: The Royal[2] and Oxford[5] studies and the Walnut Creek Contraceptive Drug Study, reported by Ramcharan et al.[11] (rated +, Table 1). The remaining studies were studies of risk factors for gallbladder disease or gallstones. The whole body of publications from these studies gives the impression that all factors studied have been reported reasonably systematically (rated +).

The funnel plot suggests that only a small degree of publication bias is present (Figure 1).

Weighting the Evidence

As we have seen so far, many studies have serious flaws in their designs. Furthermore, there may be publication bias in favor of "positive" studies on oral contraceptive use and gallbladder disease. Disregarding the "positive" studies for this reason would be inappropriate, however, because we ourselves would be guilty of introducing a biased selection of the literature. Fortunately, selection of the studies without negative ratings with respect to validity automatically excludes all studies with a negative rating for publication bias.

The 9 studies (11 publications) selected in this way are marked with an asterisk (*) in Tables 1 through 3. With one exception, the relative risks were above 1.0 (range, 1.1 to 1.6; four were statistically significant[2,12,23,24]). The exception was the study by Scragg et al. (A), showing an odds ratio of 0.7 (statistically significantly below 1.0).[15] This inconsistency is evaluated in the second part of this review.

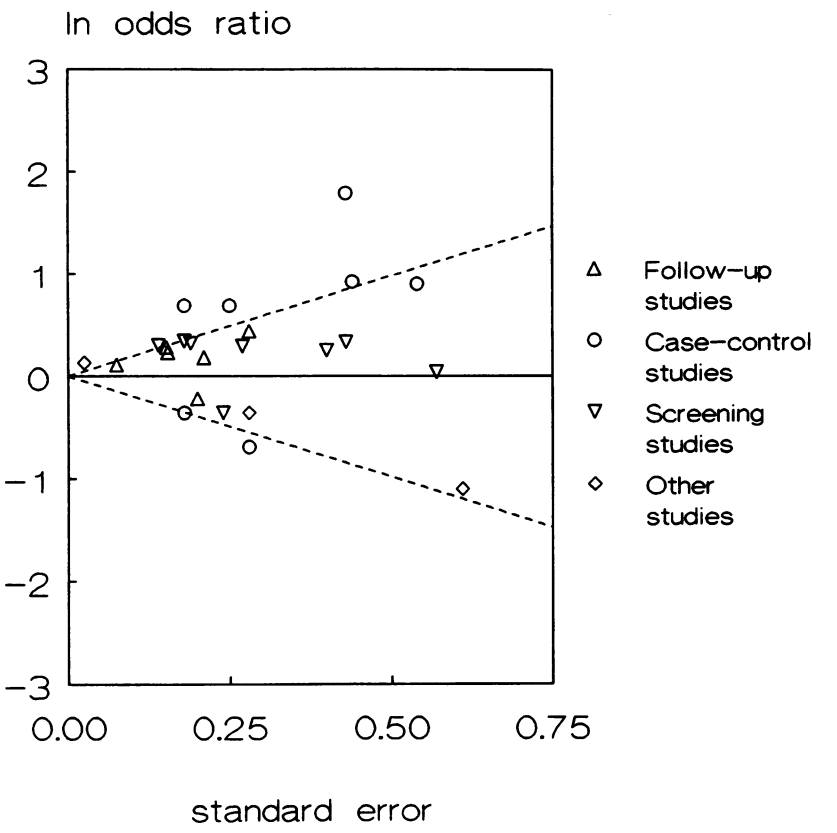
In the rest of this review, only the selected studies are considered. An exception is made for the study by Strom et al.[19]; the consistent dose–effect relationship shown by this study does not likely result from chance variation alone or from other biases.

The results of the six selected screening studies are very similar: odds ratios range from 1.3 to 1.4 (Table 3). Pooling yielded an odds ratio of 1.36 (95% confidence interval [CI] = 1.15, 1.62).

Specific Hypotheses Explaining the Inconsistencies

Is the effect restricted to biliary inflammation? The Royal study distinguished between inflammatory disease of the biliary system (cholecystitis and, occasionally, cholangitis) and gallstones without clear inflammation. In the initial report, no clear difference was found,[2] but at extended follow-up the effect was restricted to cholecystitis. For current oral contraceptive use the relative risks were 1.31 for cholecystitis (95% CI = 1.06, 1.62) and 0.95 for cholelithiasis (0.71, 1.27).[12] For former oral contraceptive use the results were comparable.

The only other study that made a similar distinction was the study by Strom et al.[19] In spite of the large number of cases,



Note. Results seem to funnel to a value slightly above ln(odds ratio) = 0, that is, an odds ratio somewhat above 1.0. Among statistically unstable results (high standard errors, right side of the plot), results below this funnel value seem to be underrepresented, suggesting publication bias. Results outside the area within dotted lines are statistically significant ($\alpha = 0.05$, two-sided).

FIGURE 1—Funnel plot of results from 24 studies on oral contraceptive use and gallbladder disease.

it did not show a difference between cholecystitis and cholelithiasis.

If oral contraceptive use causes only the formation of gallstones that become rapidly symptomatic, no effect should be found on the prevalence of asymptomatic gallstones found by screening. The same is true if oral contraceptive use causes inflammation of the gallbladder only if gallstones already exist (without itself causing gallstone formation). Neither of these possibilities can be confirmed, as two positive screening studies included only asymptomatic gallstones (Šorf et al.,[20] Maringhini et al.[21]); analyses of two other screening studies by subgroup of asymptomatic gallstones and cholecystectomy were less conclusive (GREPCO: odds ratios [95% CI] = 1.45 [0.75, 2.80] and 1.17 [0.49, 2.81], respectively[16]; Maurer et al.: odds ratios [95% CI] r = 1.2 [0.7, 1.8] and 1.8 [1.1, 2.8], respectively[24]).

To conclude, there is little evidence that oral contraceptive use causes biliary inflammation other than by causing the formation of gallstones.

Does the effect depend on age? In the study by Strom et al. the effect of oral contraceptive use decreased with age.[19] Two other studies presented age-specific results, one showing a similar trend,[15] the other a trend in the opposite direction.[23] The next section offers an explanation for age dependency.

Is the effect transient? In the Royal study the initial effect disappeared after extended follow-up.[2,12] The rate of gallbladder disease was increased only if oral contraceptive use had started within the previous 5 years, whereas it was maximal after 3 years' duration (rate ratio 1.3). In women who had used oral contraceptives for more than 7 years, the rate even dropped below that of the nonusers.[12] These findings gave rise to the following hypothesis: During the first years of oral contraceptive use the rate of gallbladder disease is raised. When women who are susceptible to gallbladder disease indeed develop the disease as a result of oral contraceptive use, the remaining population in the analysis are relatively insusceptible women. In nonusers of oral contraceptives, no such selection takes place. This would explain the lower rate of the disease at longer durations of oral contraceptive use.[12,32] The results of the Oxford study showed a similar pattern.[13]

In none of the other studies were risk periods sufficiently specified to detect a transient effect. However, the decrease of the effect with age in the study by Strom et al. may be explained by a transient effect, because the proportion of oral contraceptive users who had only recently started to use oral contraceptives must have been highest in the younger age groups.[19] A similar explanation may hold for Scragg et al.'s findings, which showed a negative association between oral contraceptives and the rate of gallbladder disease. In women aged 29 years or younger a positive relationship was found (rate ratio 1.5, 95% CI 0.2, 9.8), whereas rate ratios were below 1.0 in older age groups.[15] The latter situation may have resulted from selection of insusceptible women by earlier oral contraceptive use. However, this explanation is not entirely satisfactory, as the rate ratios in the higher age groups (which ranged from 0.5 to 0.7) were too low to have resulted from such a selection.

Selection on susceptibility occurs only when incidence density (rate ratio in follow-up studies and odds ratio in case-control studies) is measured, not when prevalence (odds ratios in screening studies) is measured. The prevalence of gallstones results from the accumulation of the rate of gallstone development over time, and gallstones are assumed to seldom disappear spontaneously. Therefore, the positive results of the screening studies do not contradict a transient effect on the rate of gallstone development.

Is the effect dose dependent? The first studies were performed at a time when oral contraceptives contained considerably larger doses of estrogen and progestin than they do now. Sub-50 oral contraceptives (containing 50 μg of estrogen or less) became available about 1975. If only higher dose oral contraceptives lead to gallbladder disease, this could explain why later studies did not find an effect. Two studies have evaluated a dose–effect relationship. In the Royal study the rate ratio in the third year of oral contraceptive use was 1.4 at 50 μg of estrogen and 3.2 at 100 or 150 μg.[12] However, these

results were based on a few cases only. Strom et al. confirmed a dose–effect relationship with estrogen dose: relative risks (95% CIs) for estrogen doses of less than 50 μg, 50 μg, and more than 50 μg were 1.0 (0.9, 1.04), 1.1 (1.06, 1.19), and 1.2 (1.08, 1.35), respectively (trend $P = .001$).[19] In younger women the dose–effect relationship was more pronounced, whereas it was absent in older women. This age dependency may be due to transiency of the effect. In none of the studies was it possible to control for different effects of the progestin component of these formulas.

Discussion

In 25 epidemiologic studies of oral contraceptive use and gallbladder disease, the results were highly inconsistent. Nine of these studies could stand the test of critical appraisal with respect to internal validity. We argue that restricting our analysis to these studies circumvented publication bias. This selection of studies showed much more consistent results. The evidence confirmed a transient effect of oral contraceptive use on the rate of gallbladder disease, with a dose–effect relationship with estrogen dose. However, it is not clear whether this relationship is due to the estrogen or the progestin component, or to differences in the generic characteristics of the components. The inconsistency between the study by Scragg et al. and the other selected studies could (at least partly) be explained by selection on the basis of susceptibility in combination with a transient effect. In studies not affected by such selection (screening studies), the results were strikingly homogeneous, justifying statistical pooling (pooled odds ratio = 1.36).

All of the studies reviewed failed to specify risk periods. This failure makes it difficult to disentangle the effects of decreasing dose through time, duration of oral contraceptive use, transiency of the effect, and increasing prevalence of gallstones by age. Moreover, it may hamper control of confounding by time-dependent factors such as pregnancy. In a previous study we showed that the effect of pregnancy is limited to some 5 years after pregnancy, and that this effect is missed if risk periods are ignored.[38] Any further study of oral contraceptive use and gallbladder disease should more properly specify risk periods. Because such specification is also a prerequisite for the estimation of excess risk,[39] computing excess risk from the results of the studies reviewed here would be fallacious, and therefore we have not done so.

The latency period between gallstone formation and symptomatic gallstone disease has been reported to average 12 years (range, 2 to 20 years).[40] The transiency of the effects of oral contraceptive use within 5 or 10 years sharply contrasts to this latency period. This discrepancy suggests that oral contraceptive use enhances the development of symptoms of already existing gallstones, with or without enhancing gallstone formation. It has been speculated that mechanisms involved in the formation of gallstones (increased biliary cholesterol saturation and decreased gallbladder motility) also play a role in gallbladder inflammation.[41] However, there is no empirical support for this explanation in the studies reviewed here. In particular, if oral contraceptive use did lead to an excess rate of cholecystectomy higher than an excess rate of gallstone formation, no association should have been observed between oral contraceptive use and prevalence of gallstones in the screening studies.

The effect of oral contraceptive use on gallstone formation is (at least partly) mediated by an increase of biliary cholesterol saturation[28,32] and possibly also by alteration of gallbladder function.[42–44] Serum lipids may play a role in the first mechanism.[45] Many modern oral contraceptives are designed to have no adverse influence on serum lipids (i.e., no decrease of high-density lipoprotein or increase of triglyceride levels). Avoidance of such influence may prevent gallstone formation. However, too little is known about the causality of the relationship between serum lipids and biliary cholesterol saturation to be confident of this theory. A metabolic study has shown that low-dose oral contraceptives increase bile saturation.[46] This effect was judged to be quantitatively similar to that of older high-dose pills.[46] No influence was observed on gallbladder motility. The quantitative importance of either mechanism on the development of gallstones, and their role in the development of symptoms, is not known. Therefore, although the epidemiologic evidence suggests a smaller effect of modern low-dose oral contraceptives than of older oral contraceptives, an effect on gallbladder disease cannot be excluded at the moment. Considering the large efforts already devoted to studying the relationship between oral contraceptive use and gallbladder disease, the probably weak effect, and the rapidly changing formulas of oral contraceptives, we suggest that the safety of new oral contraceptives be evaluated by studying bile saturation and biliary function rather than by waiting for gallbladder disease to develop. □

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