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Safety of hormonal contraception among women with liver disease: an updated systematic review

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Abstract

Objectives: We sought to assess whether, among women with liver disease, there is an increased risk of adverse health effects with the use of hormonal contraception (HC).

Study design: We conducted a systematic review of six databases from database inception through December 13, 2022. We searched for articles that examined changes in liver lesions and acute and chronic liver disease with the use of HC or after discontinuation of HC. We assessed the risk of bias for each study and certainty of evidence for all outcomes.

Results: Thirteen articles met inclusion criteria, one with low risk of bias and the others with high risk of bias: three studies (four articles) were of women with focal nodular hyperplasia (FNH), five studies were of hepatocellular adenoma (HCA), and four studies were of acute or chronic hepatitis. The size and/or number of FNH lesions were generally not influenced by HC use. HCA progression was generally higher among current combined oral contraception (COC) users than those who discontinued, and lesions were stable or regressed in most women who discontinued COC or used progestin-only contraception. Studies found that viral hepatitis generally did not progress or increase in severity with the use of COC.

Conclusion: Overall, a limited body of evidence suggested changes in FNH lesions were independent of hormonal contraceptive use. Estrogen-containing contraceptive method use was associated with HCA lesion progression; lesions generally remained stable with progestin-only contraceptive use. COC use did not increase progression or severity of disease among those with viral hepatitis. The certainty of evidence for all outcomes was very low.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or International Planned Parenthood Federation.

CRediT authorship contribution statement

N.K.T.: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. S.G.: Validation, Formal analysis, Data curation. A.T.N.: Methodology, Investigation, Data curation, Conceptualization. K.M.C.: Supervision, Resources, Methodology. K.K.: Validation, Formal analysis, Data curation. M.K.W.: Writing – original draft, Formal analysis, Data curation. N.K.: Writing – original draft, Methodology, Data curation.

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Implications: Liver conditions such as liver lesions, viral hepatitis, and cirrhosis are increasingly common in women of reproductive age. Information in this review can be used by health care providers when counseling women with liver disease about the safe use of contraception.

Keywords

Combined oral contraception; Focal nodular hyperplasia; Hepatitis; Hepatocellular adenoma; Hormonal contraception; Liver disease; Systematic review

1. Introduction

Approximately 4.5 million adults in the United States are living with liver disease, and chronic liver disease was the ninth leading cause of death in 2021 [1]. Liver disease is increasingly common among women of reproductive age, and consideration of safe and effective contraceptive use is important for those who wish to avoid pregnancy [2]. Hormonal methods of contraception have effects on and are metabolized by the liver; thus, consideration of the severity of existing disease is important in determining the risks, benefits, and a woman's medical eligibility for hormonal contraception (HC). Estrogen-containing drugs have direct receptor-mediated impact on hepatocytes, whereas progestins do not. However, some noncontraceptive formulation progestins at high doses may be metabolized into estrogenic compounds [3–6]; thus, there are theoretical concerns of impaired hepatic metabolism of exogenous hormones in women with liver dysfunction and that use of HC in the setting of liver disease may worsen liver function and affect disease progression.

Two benign lesions of the liver are hepatocellular adenomas (HCAs) and focal nodular hyperplasia (FNH). HCAs have a rare risk of hemorrhage or malignant transformation. Increased exposure to estrogen from combined hormonal contraception (CHC) and from obesity has been associated with development and growth of HCAs [7]. Unlike for HCA, the relationship between the development of FNH and estrogen exposure is not clearly established [8].

Both infectious and noninfectious agents can lead to hepatitis. These processes may eventually cause fibrosis, leading to cirrhosis, compromised liver function, and even death [9]. Globally, an estimated 354 million people worldwide are living with hepatitis B or C, the most common causes of chronic viral hepatitis [10]. Among them are approximately 65 million women of reproductive age with hepatitis B [11]. In the United States, among women of reproductive age, the annual rate of acute hepatitis B infections has been stable nationally but increased in several states during 2011–2017 [12]. Rates of hepatitis C are increasing in the United States among women of reproductive age. Confirmed hepatitis C among women aged 18–44 years doubled during 2006–2014 [13]. Prevention of unintended pregnancy, along with other strategies to improve screening and timely treatment, are important to minimize vertical transmission of hepatitis B and C [14].

The US Centers for Disease Control and Prevention publishes the *US Medical Eligibility Criteria for Contraceptive Use* (US MEC) [15], which provides evidence-based guidance on the safety of contraceptive methods for patients with certain characteristics or medical

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conditions, including liver disease. As part of a process to update the US MEC, the objective of this systematic review was to assess whether, among women with liver disease, there is an increased risk of adverse health effects among those using HC (by formulation and type) compared with those who are using non-HC or not using contraception. This review updates two previous systematic reviews on HC safety among those with liver disease [16,17].

2. Methods

This systematic review was conducted according to an a priori protocol, which has been registered in the International Prospective Register of Systematic Reviews under the registration number CRD42019127163 [18] and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [19].

2.1. Eligibility criteria

Studies were eligible for inclusion if they examined the safety of HC use by women with liver disease. The population of interest was women with liver disease, including liver lesions, viral hepatitis (acute or chronic), and cirrhosis. The exposure of interest was the use of any HC, including CHC (i.e., combined oral contraception [COC], transdermal patch, or vaginal ring) or progestin-only contraception (POC; i.e., levonorgestrel intrauterine device [LNG-IUD], implant, progestin-only injectables, or progestin-only pill [POP]). We also included studies of women who discontinued HC use at or after liver disease diagnosis. The comparison of interest was the use of nonhormonal or no contraception, including discontinuation. The outcome of interest was changes in liver disease, as measured by liver function, liver fibrosis, malignant transformation, flare of chronic viral hepatitis B or C, or lesion number or size/volume. We included the following study designs: randomized trials, non-randomized trials, cohort studies (comparative and noncomparative), case-control studies, and cross-sectional studies. We excluded case reports and review articles.

2.2. Search strategy

We worked with a research librarian at the US Centers for Disease Control and Prevention to develop the search strategy (Appendix A). The search was conducted in MEDLINE, Embase, Global Health, the Cochrane library, ClinicalTrials.gov, and CINAHL databases from database inception to December 13, 2022. We reviewed references in systematic reviews to optimize our search. Articles in all languages were considered. We did not consider unpublished studies or abstracts.

2.3. Study selection and data extraction

Among articles identified by the search strategy, all titles and abstracts were screened independently by at least two co-authors, using the Covidence platform [20]. Two co-authors then reviewed full-text articles to determine if they met the inclusion criteria. Any conflicts were resolved by discussion. We used standardized evidence tables to summarize information on each study.

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2.4. Risk of bias assessment

We assessed the risk of bias using a modified version of the Cochrane approach [21], including risk of selection bias, information bias for exposure and outcomes, and confounding. Two co-authors independently assessed the risk of bias for each included study, and conflicts were resolved by discussion.

2.5. Data synthesis

We summarized descriptive statistics, unadjusted and adjusted point estimates, and results of significance tests. We did not conduct meta-analyses due to heterogeneity of study populations, exposures, and outcomes.

2.6. Certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess certainty of evidence for all outcomes of interest [22–24]. For each outcome, we considered risk of bias, directness, precision, and consistency to be not serious, serious, or very serious. Based on these assessments, the certainty of evidence was rated as high, moderate, low, or very low. At baseline, randomized controlled trials are considered to have high certainty and observational studies are considered to have low certainty; ratings are then adjusted based on the criteria previously listed.

3. Results

We screened 5507 articles, from which 164 articles were identified for full-text review (including one article [25] identified from a reference list of an included article; Fig. 1). Among these, 151 were excluded (96 wrong study design, 37 wrong patient population, nine wrong intervention, five wrong outcomes, and four abstract only). A total of 13 articles met the inclusion criteria [25–37]; two of these described data from one study [32,33]. Two articles from the previous reviews were excluded: one for wrong patient population (subjects with previous but not necessarily chronic hepatitis) [38] and one for wrong intervention (unknown HC exposure during follow-up period) [39].

Eight studies (nine articles) reported on women with liver lesions, including three studies (four articles) on women with FNH [26,30,32,33] and five studies on women with HCA [25,27,31,34,36] (Table 1). Among the studies on women with FNH, two (three articles) were comparative cohort studies [26,32,33] and one was a case-control study [30]. Women used COC [26,32,33], POP [32,33], or oral contraception (OC; type not specified but presumed mostly COC) [30]. Outcomes reported were changes in lesion number and size (progression and regression). Among the studies on women with HCA, two were comparative cohort [34,36] and three were noncomparative cohort studies [25,27,31]. Women used COC [31,34], POC (LNG-IUD, implant, depot medroxyprogesterone acetate [DMPA], or POP) [27,34], or OC (type not specified but presumed mostly COC) [25,36]. In one of these studies, some women were using noncontraceptive hormone formulations (e.g., menopausal hormone therapy) or doses (e.g., high-dose progestins for abnormal bleeding), and results were not reported separately for contraceptive formulations or doses; however, approximately 75% of participants were using contraceptive formulations [34].

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In two studies, some women used COC containing estrogen at higher doses (≥50 mcg ethinyl estradiol) than those currently used [31–33]. Outcomes reported were lesion changes (progression and regression) and malignant transformation. One of the studies on FNH [30] and all the studies on HCA were newly identified since the previous systematic review [17]. We did not identify studies of HC use among women with malignant liver lesions.

Four studies reported on women with hepatitis [28,29,35,37], including hepatitis B [35,37], hepatitis C [28], or type unspecified [29] (Table 2). One was a nonrandomized trial [37], two were comparative cohort studies [28,35], and one was a noncomparative cohort study [29]. All studies examined COC use, except one study that did not specify OC type, but we presumed it to be mostly COC [35]. In one study, COC contained estrogen at higher doses (50 mcg ethinyl estradiol) or different formulations (mestranol) than those currently used [29]. Outcomes reported were changes in liver enzymes, hepatic fibrosis, and clinical course. All studies were included in the previous systematic review. No evidence was identified on women with cirrhosis, consistent with the previous review [16].

3.1. Risk of bias

The risk of bias for all studies of FNH was high (Fig. 2) [26,30,32,33]. All studies had limited assessment of HC without validation (only self-report) and reported crude risk estimates only without adjustment for confounders. The risk of bias for four of five studies of HCA was also high (Fig. 2) [25,31,34,36]. The non-randomized comparative studies reported crude risk estimates only without adjustment for confounders [34,36]. Two of the noncomparative cohort studies lacked description of the formulations of contraceptive methods [25,31], and one study additionally had a low rate of follow-up [25]. The risk of bias for all studies of hepatitis was high (Fig. 3) [28,29,35,37]. The nonrandomized comparative studies had high risk of selection bias and reported crude risk estimates only without adjustment for confounders [28,35,37]. The noncomparative cohort study had a low rate of follow-up [29].

3.2. Summary of results on liver lesions

Three studies (four articles) reported changes in FNH number or size with use of OC [26,30,32,33]. One comparative cohort study (two articles) examined 136 women with FNH, including those with current COC use ($n = 26$), discontinuation of COC use (after FNH diagnosis; $n = 89$), current POP use ($n = 7$), and no OC use ($n = 14$), followed for a mean of 23 months (range 6 months to 9 years) [32,33]. All women had a decrease or no change in the size and number of lesions, except for one woman (1%) who discontinued COC and experienced an increase in the size of one lesion (no statistical testing reported). Another comparative cohort study examined 23 women with FNH, including those with current COC use ($n = 2$) or those who discontinued COC use (at FNH diagnosis; $n = 21$), followed for a median of 45 months [26]. Lesion size decreased or was stable in most women, but lesion size increased in one current user (50%) and in three discontinuers (14%; no statistical testing reported). A case-control study examined 95 women with FNH, followed for a mean of 19 months [30]. The percent using OC (type not specified) was not statistically significantly different among cases who had lesion growth and controls who did not (29% vs 32%, $p = 0.83$).

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Five studies reported on HCA lesion changes with use of COC, POC, or OC type not specified [25,27,31,34,36], and four studies also reported on incidence of malignant transformation [27,31,34,36]. One comparative cohort study examined 63 women with HCA, 27 who were currently using OC (type not specified), and 36 who discontinued OC use (after HCA diagnosis) during a mean of 35 months of follow-up [36]. HCA progression was higher among current users than among discontinuers (33% vs 3%, $p = 0.001$). There was one malignancy during follow-up; it was not reported whether this was in a current COC user or discontinuer. The other comparative cohort study examined 27 women with HCA and estrogen use ($n = 7$; six COC users and one user of estradiol for menopausal symptoms), progestin-only use ($n = 8$; three LNG-IUD users, one DMPA user, one implant user, one user of oral medroxyprogesterone for amenorrhea, and two users of norethindrone oral 5–15 mg for menorrhagia), and no hormonal use ($n = 19$) [34]. Estrogen users had an increase in the sum of lesion diameters (median 29.4%) between baseline and follow-up imaging. Progestin-only users and nonhormonal users had a decrease in the sum of lesion diameters (median 15.0% and 7.4%, respectively). The changes in lesion diameters were significantly different between estrogen users (increased) and progestin-only users (decreased; $p = 0.04$). The decreases in size were not significantly different between progestin-only and nonhormonal users. Statistical comparisons of size differences among estrogen users (increased) and nonhormonal users (decreased) were not reported. No malignant transformation occurred in any hormonal user. One noncomparative cohort study examined 96 women with HCA who discontinued OCs (type not specified; at HCA diagnosis); follow-up duration was not reported [25]. Regression of lesions was found in 76 women (79%) after OC discontinuation. Another noncomparative cohort study examined 78 women with HCA who discontinued COC use (after HCA diagnosis), followed for a median of 1.1 years [31]. Lesion size was unchanged (44/78, 56%), decreased (29/78, 37%), or resolved (4/78, 5%) in most women after COC discontinuation, with one exception (1%). No malignant transformation occurred during follow-up. The third noncomparative cohort study examined 13 women with HCA among POC users (seven LNG-IUD users, two implant users, and eight POP users), followed for a median of 2 years [27]. All experienced regression or no change, excepting one (8%) who experienced progression. No malignant transformation occurred during follow-up.

3.3. Summary of results on viral hepatitis

Four studies reported on changes in liver enzymes, hepatic fibrosis, or clinical course with use of COC or OC type not specified among women with hepatitis [28,29,35,37]. One nonrandomized trial examined 115 women with chronic hepatitis B and compared COC users ($n = 78$) to users of other contraception (type not specified; $n = 81$) [37]. At 3 and 6 months of follow-up, there were no clinical symptoms or signs of hepatitis or hepatomegaly and no significant differences in liver enzyme values between groups. One comparative cohort study examined 68 women with acute hepatitis, 51% of whom had hepatitis B and compared the use of OC (type not specified; $n = 34$) to nonuse ($n = 34$) during 1 year of follow-up [35]. No differences in liver function tests, hospitalization days, or clinical course between groups and no progression to chronic disease occurred in either group. The other comparative cohort study examined 157 women with chronic hepatitis C and compared OC use ($n = 105$; 94% COC and 6% POP) to nonuse ($n = 52$) [28]. The mean fibrosis score was

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lower in OC users than nonusers (1.38 vs 1.80, $p = 0.02$), with no significant differences in grade of necroinflammatory activity or rate of hepatic fibrosis. One noncomparative cohort study examined 10 women who started COC 2 weeks after normalization of liver enzymes following viral hepatitis (type not specified) [29]. All women had normal liver enzymes after 2–3 months of follow-up.

3.4. Certainty of evidence

The certainty of evidence for liver lesions based on studies of women with FNH and HCA was assessed as very low [40]. For all outcomes, we had serious or very serious concerns for risk of bias due to selection bias, information bias, and crude estimates without adjustments for known confounders. There were very serious concerns for imprecision due to small sample sizes and no power calculations. There were no serious concerns for inconsistency or indirectness. The certainty of evidence for hepatitis was also assessed as very low [40]. For all outcomes, there were very serious concerns for risk of bias due to selection bias, information bias, and crude estimates. There were very serious concerns for imprecision due to small sample sizes and no power calculations. There were no serious concerns for inconsistency or indirectness.

4. Discussion

The evidence indicates that FNH and HCA might respond differently to exogenous hormones. Changes in FNH lesions were generally independent of HC use, with lesions demonstrating increases, decreases, or no change during COC or POP use and after COC discontinuation. Studies found that HCA lesions were generally estrogen responsive. HCA lesion progression was more likely among COC users than nonusers, and lesion size generally decreased with discontinuation. HCA lesion changes among POC users were similar to nonusers. The evidence suggested that COC use does not increase progression or severity of disease among women with hepatitis B or C, while there was no evidence on cirrhosis.

The role, if any, of HC in the progression of liver disease to hepatocellular carcinoma remains unclear. As HCA may progress to hepatocellular carcinoma (generally 5% of cases) [41], hormonal impact on HCA size and volume may theoretically alter the risk of progression to cancer. Only one case of HCA transformation to hepatocellular carcinoma was documented in the four studies reporting on this outcome, and it is not clear whether this occurred in a current or former OC user [36].

The new evidence we reported was from studies conducted among women with either FNH or HCA liver lesions. FNH is a relatively common liver lesion that is more prevalent among women than men; however, the role of sex hormones in etiology or development is unclear [8]. One new study on FNH was consistent with two previously included studies in finding that FNH lesions appeared to stabilize or change regardless of HC use or discontinuation [26,30,32,33], which may suggest HC use does not play an important role. However, data from five newly identified studies of women with HCA demonstrated greater progression with estrogen exposure and greater regression with its discontinuation when compared with progestin-only methods or no hormonal use [25,27,31,34,36].

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The body of evidence on the safety of HC in women with liver disease has several limitations, and we rated it as very low for all outcomes. Most studies had a high risk of bias. Several studies did not specify contraceptive formulation or examined older formulations. Older formulations of contraceptives, however, included higher estrogen doses; newer formulations with lower doses of ethinyl estradiol or newer estrogen formulations may have less impact on liver function. Generalizability is limited because most studies had small sample sizes of mostly homogenous populations lacking a variety of liver disease etiologies. In addition, our interpretation of several studies is limited by lack of a comparison group.

Drug metabolism may be impaired in patients with significant liver dysfunction [42], with HC use, leading to increased exposure to exogenous hormones. Furthermore, elevated levels of exogenous hormones could theoretically increase risk for hormone-related side effects and adverse events, such as thromboembolism. Estrogen-containing formulations are associated with increased risk of thromboembolism compared with nonuse [43–46]. In addition, DMPA is a relatively higher dose than other POCs, and its use has been associated with a higher risk for venous thrombosis compared with nonuse [47–49]. Future study of thrombosis risk in women with liver disease who use HC is needed.

In conclusion, a limited body of evidence suggested that changes in FNH lesions were independent of HC use. COC use was associated with HCA lesion progression, but generally remained stable with POC use. COC use did not increase progression or severity of disease among those with chronic hepatitis. This information was reviewed for the US MEC 2024 [15].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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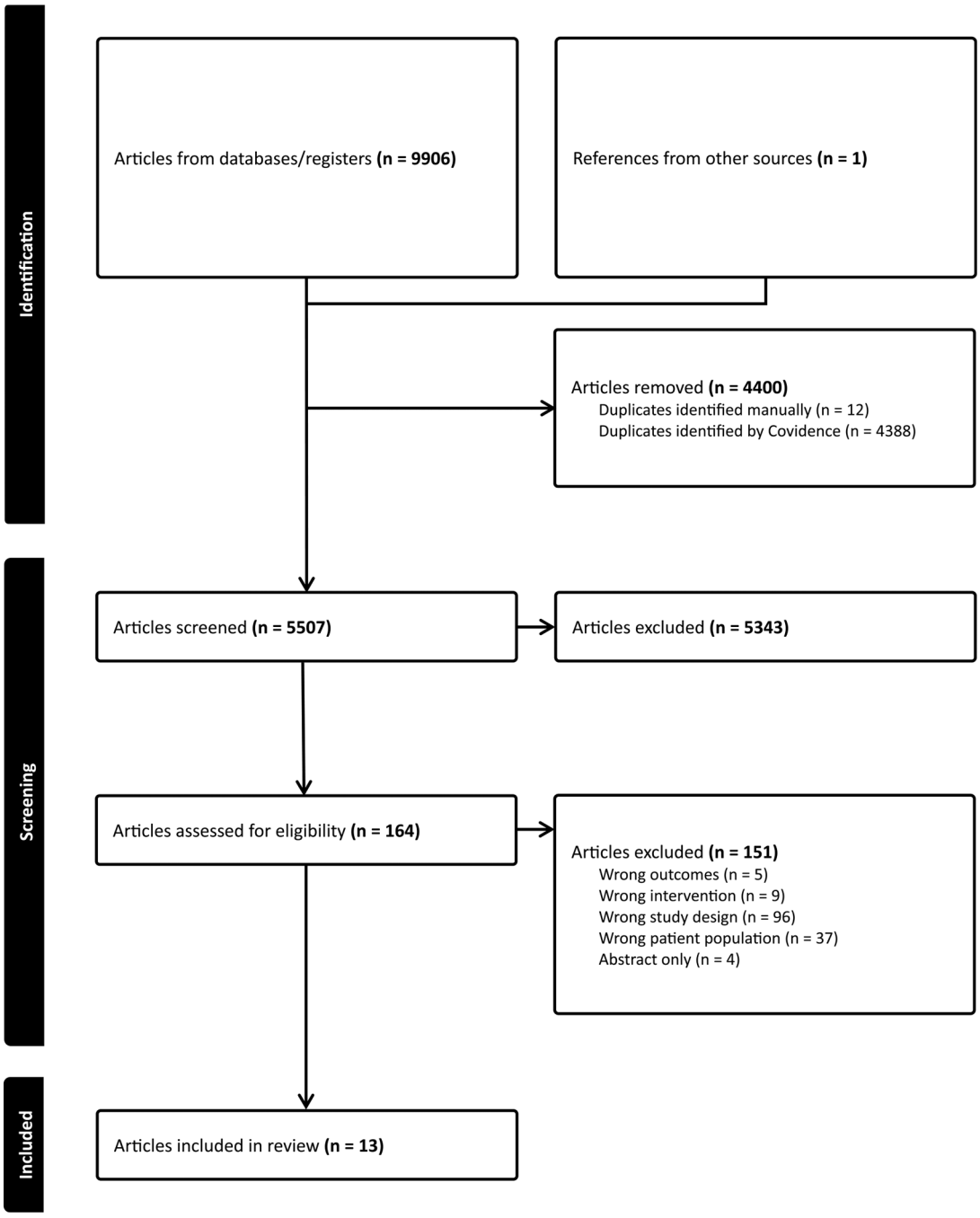


Fig. 1.

PRISMA flowchart for the search process for evidence on the safety of hormonal contraception among women with liver disease. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

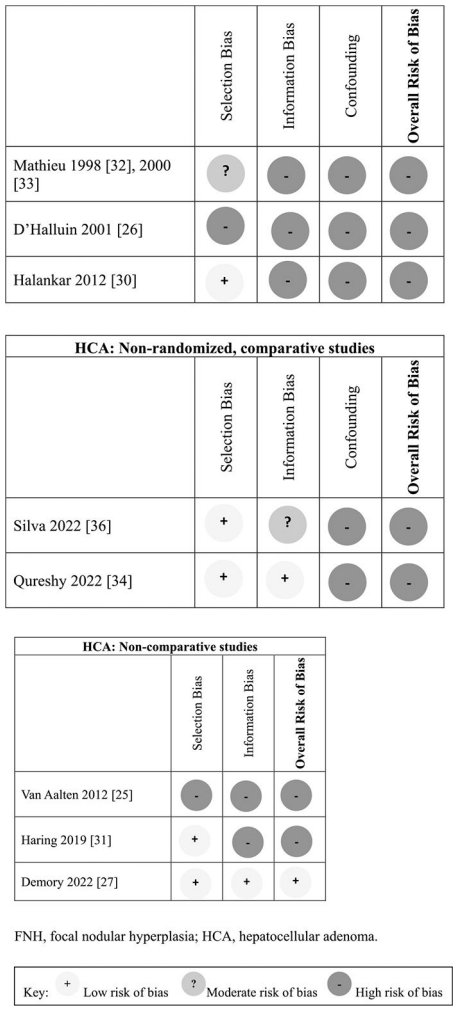


Fig. 2.
Risk of bias for studies on liver lesions.

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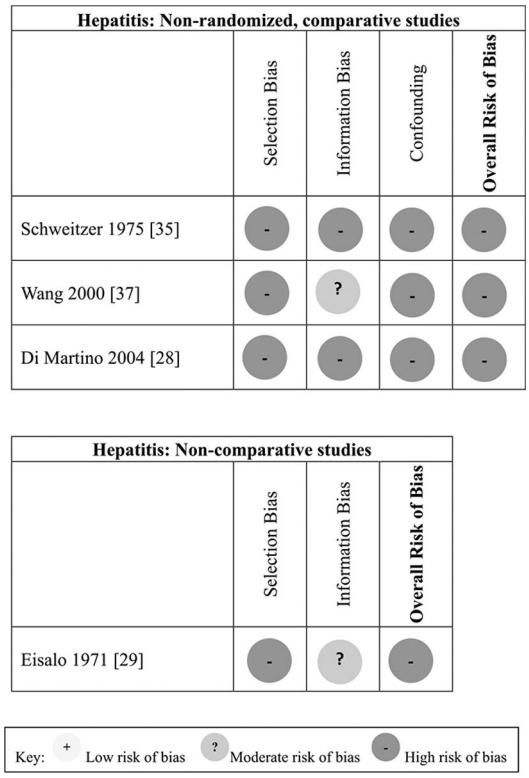


Fig. 3.
Risk of bias for studies on hepatitis.

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Table 1

Evidence on changes in liver lesions with use of hormonal contraception

Author, year, location, funding	Study design, timing of data collection, follow-up	Study population	Contraceptive exposure after diagnosis and comparison	Outcome, outcome assessment	Results
Focal nodular hyperplasia (FNH)					
Mathieu, 1998 [32], 2000 [33] France Funding not reported	Comparative cohort 1989–1998 Follow-up: mean 23 mo (range 6 mo to 9 y)	136 women with ≥1 FNH, ages 14–70 y	COC use (n = 26) POP use (n = 7) Discontinued COC use after FNH diagnosis (timing not specified; n = 89) No OC use (n = 14) COCs contained ≥50 μg EE or ≤30 μg EE or successive use of both POP type not specified	Change in FNH lesion number or size MRI	COC use: • No change: 25/26 (96%) • Resolution: 1/26 (4%) POP use: • No change(100%) Discontinued COC: • Increase: 1/89 (1%) • No change: 86/89 (97%) • Decrease: 2/89 (2%) No OC use: • No change(100%) No statistical testing was reported.
D'Halluin, 2001 [26] France Funding not reported	Comparative cohort Time of data collection not reported Follow-up: Median 45 mo	23 women, median age 35 y, with ≥1 FNH for more than 1 y	Continued COC use (n = 2) Discontinued COC use at FNH diagnosis (n = 21) COC contained "mini" estrogen doses or > 40 μg EE	Change in FNH lesion number or size Ultrasound	Continued COC use: • Increase: 1/2 (50%) • Decrease: 1/2 (50%) Discontinued COC: • Increase: 3/21 (14%) • No change: 11/21 (50%) • Decrease: 7/21 (34%) No statistical testing was reported.
Halankar, 2012 [30] Canada No funding received	Case-control Time of data collection not reported Follow-up: mean 19 mo	95 women, ages 18–−80 y (mean 45 y), with FNH and at least two MRI scans 6 mo apart Cases: those with increased lesion size (n = 17) Controls: those with no growth in lesion size (n = 78)	OC use during follow-up OC type not specified	Change in FNH lesion size MRI	Increased lesion size • OC use: 5/17 (29%) No growth in lesion size • OC use: 25/78 (32%) p = 0.83
Hepatocellular adenoma (HCA)					
Van Aalten, 2011 [25] The Netherlands No funding received	Noncomparative cohort 2000–2009 Follow-up time not reported	96 women with HCA	Discontinued OC use at HCA diagnosis OC type not specified	Change in HCA lesion size Radiologic imaging, histopathology	76/96 (79%) with regression
Haring, 2019 [31] The Netherlands Funding not reported	Noncomparative cohort 2005–2018 Follow-up: median 1.1 y	78 women with HCA	Discontinued COC use after HCA diagnosis (timing not specified) COC contained 50 μg estrogen in 3.8%, unknown estrogen dose in 26.9%, and < 50 μg in remaining	Change in HCA lesion size Malignant transformation	Progression: 1/78 (1%) Stable: 44/78 (56%) Partial response: 29/78 (37%) Complete response: 4/78 (5%) No malignant transformation

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Author, year, location, funding	Study design, timing of data collection, follow-up	Study population	Contraceptive exposure after diagnosis and comparison	Outcome, outcome assessment	Results
				CT or MRI, histopathology	
Silva, 2022 [36] USA No funding received	Comparative cohort 2008–2017 Follow-up: mean 35 mo, five imaging studies	63 women with HCA	OC use (n = 27) Discontinued OC use after HCA diagnosis (timing not specified; n = 36) OC type not specified	Change in HCA lesion size at least 6 mo after OC cessation Malignant transformation CT or MRI, histopathology	Continued vs discontinued OC use: • Progression: 33% vs 3% (p = 0.001) • Stable: 52% vs 78% (p = 0.06) • Regression: 15% vs 19% (p = 0.74) 1 malignancy, not stated whether OC user or discontinuer
Demory, 2022 [27] France PRENEO INCA PREMALHEP	Noncomparative cohort 2000–2019 Follow-up: median 2 y for entire cohort	13 women with HCA	POC (n = 17) LNG-IUD (n = 7) Implant (n = 2) POP (n = 8) POC users (n = 17) included women with residual HCA who used POC (n = 13) and four additional women who used POC after HCA diagnosis; further detail not provided	Change in HCA lesion size Malignant transformation CT or MRI, histopathology	Progression: 1/13 (7.7%) Stable: 10/13 (76.9%) Regression: 2/13 (15.4%) No malignant transformation
Qureshy, 2022 [34] USA National Institute of Diabetes and Digestive and Kidney Diseases; University of California San Francisco Liver Center	Comparative cohort 2003–2021 Follow-up: median 11 mo	27 women with HCA, ages 16–45y (mean 33.5y) 34 time intervals analyzed	Estrogen (n = 7) *COC* (n = 6) Transdermal estradiol patch (n = 1) Progestin (n = 8) LNG-IUD (n = 3) DMPA (n = 1) Oral medroxyprogesterone (5 mg; n = 1) Etonogestrel implant (n = 1) Norethindrone (5–15 mg; n = 2) No hormone use (n = 19)	Change in HCA lesion size, reported as change in sum of HCA diameters, median % change Malignant transformation CT or MRI, histopathology	Estrogen: • 29.4% (IQR 17.4–140.4) Progestin: • −15% (IQR −24.4 to −5.9; p = 0.52 compared with no use p = 0.04 compared with estrogen exposure) No hormone use: • −7.4% (IQR −17.6 to −27.9) No malignant transformation

COC, combined oral contraception; CT, computerized tomography; DMPA, depot medroxyprogesterone acetate; EE, ethinyl estradiol; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; IQR, interquartile range; LNG-IUD, levonorgestrel intrauterine device; MRI, magnetic resonance imaging; OC, oral contraception; POC, progestin-only contraception; POP, progestin-only pill.

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Table 2

Evidence on adverse viral hepatitis outcomes with use of hormonal contraception

Author, year, location, funding	Study design, timing of data collection, follow-up	Study population	Exposure and comparison	Outcome, outcome assessment	Results
Eisalo, 1971 [29] Finland	Noncomparative cohort Timing of data collection not reported	10 women, 2 wk after resolution of acute hepatitis	COC use (n = 10) COC contained 50 μg EE or 75 μg mestranol	Serum transaminase testing every 2 wk	All women after 4 wk had normal transaminase levels; few mild elevations prior to the end of first month of use
Funding not reported Schweitzer, 1975 [35] USA Funding not reported	Follow-up: up to 9 wk Comparative cohort 1972–1974 Follow-up: 1 y	68 women admitted for acute hepatitis, 51% with HBV	OC use (type not specified; n = 34) No OC use (age matched; n = 34)	AST/ALT and clinical follow-up 2 wk, 2 mo, 5 mo, 1 y	No difference in AST/ALT between groups Hospitalization days: OC 12.2 vs non-OC 12.4 (p = 0.92) No chronic liver disease
Wang, 2000 [37] China Funding not reported	Nonrandomized trial Unknown to 1995 Follow-up: 6 mo	115 patients with chronic HBV	COC use (n = 78) “Other” contraception (n = 81) COC contained 30 μg EE plus 150 μg LNG	AST/ALT at 3 mo and 6 mo	Normal AST/ALT at 3 and 6 mo, no differences between COC users and “other” users at any time point (p > 0.05); one transient elevation in ALT in COC group at 3 mo
Di Martino, 2004 [28] France Funding not reported	Comparative cohort 1993–2001 Follow-up: up to 7y	157 women with chronic HCV	OC use (n = 105) (COC in 94%, POP in 6%) No OC use (n = 52) COC contained 30 μg EE in 70% and 50 μg EE in 40%, some women used both	Necroinflammatory activity Mean fibrosis score Rate of hepatic fibrosis	OC users vs nonusers: • Grade of necroinflammatory activity 1.18 vs 1.18 (NS) • Mean fibrosis score 1.38 vs 1.80 (p = 0.02) • Rate of hepatic fibrosis 108 vs 115 (NS)

AST/ALT, aspartate aminotransferase/alanine aminotransferase; COC, combined oral contraception; EE, ethinyl estradiol; HBV, hepatitis B virus; HCV, hepatitis C virus; LNG, levonorgestrel; NS, nonsignificant; OC, oral contraception; POP, progestin-only pill.

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