Contraception with levonorgestrel-releasing intrauterine system versus copper intrauterine device: a meta-analysis of randomized controlled trials

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Summary

Background Globally, approximately 19.4% of women of reproductive age use intrauterine contraception, encompassing both copper intrauterine devices (Cu-IUDs) and levonorgestrel intrauterine devices (LNG-IUDs). Despite current guidelines endorsing intrauterine contraception as a primary method, there remains debate regarding device selection. Notably, the lack of data regarding reasons for discontinuation has limited previous meta-analyses. This study aims to comprehensively evaluate the potential differences between intrauterine devices using available multinational data, thereby providing a basis for global policy and healthcare services.

Methods We systematically searched PubMed, EMBASE, Web of Science, and Cochrane Library for primary studies published from inception to January 13, 2024, with no language or geographic restrictions. The study was registered on PROSPERO (CRD42024496400). We included only randomized controlled trials comparing Cu-IUDs and LNG-IUDs. Data extraction was independently conducted by two reviewers, with unresolved discrepancies referred to a third senior reviewer for consultation. The primary outcome was pregnancy, with secondary outcomes encompassing continuation, reasons for discontinuation, expulsion, satisfaction, and other adverse events. Data were synthesized using a random-effects model. Risk of bias was evaluated with the Cochrane Collaboration's tool, and evidence quality was assessed using the GRADE framework.

Findings An analysis of 20 trials showed that compared to Cu-IUDs, LNG-IUDs were associated with lower risks of pregnancy (Risk Ratio 0.22, 95% confidence interval 0.12–0.39), ectopic pregnancy (RR 0.12, 95% CI 0.03–0.47), discontinuation due to increased bleeding (RR 0.49, 95% CI 0.28–0.85), increased bleeding (RR 0.42, 95% CI 0.25–0.7), heavy bleeding (RR 0.41, 95% CI 0.22–0.75), and dysmenorrhea (RR 0.41, 95% CI 0.34–0.48), but they carried a higher risk of discontinuation due to amenorrhea (RR 21.05, 95% CI 8.83–50.00). When comparing LNG (52 mg) IUD with copper (380 mm^2) IUD, The LNG-IUD showed a lower risk of discontinuation due to increased bleeding (RR 0.68, 95% CI 0.55–0.58) and dysmenorrhea (RR 0.42, 95% CI 0.34–0.53), but a higher risk of discontinuation due to bleeding issues (RR 2.83, 95% CI 2.47–3.25) and amenorrhea (RR 5.92, 95% CI 2.81–12.49). There were no significant differences between the two terms of continuation, expulsion, non-medical reasons for discontinuation, satisfaction, and other adverse outcomes.

Interpretation LNG-IUDs and Cu-IUDs are both highly effective contraceptive methods. Compared to Cu-IUDs, LNG-IUDs were associated with a lower risk of pregnancy and adverse reactions. However, LNG-IUDs carry a higher risk of amenorrhea. When recommending contraceptive methods, healthcare providers should fully inform patients of these potential risks and consider patient preferences.

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Research in context

Evidence before this study

In a 2004 meta-analysis, French and colleagues combined four relevant randomized controlled trials and found that LNG-IUDs releasing 20 μg of levonorgestrel per day demonstrated greater effectiveness in preventing both intrauterine and ectopic pregnancies compared to Cu-IUDs ≤250 mm^2. However, there was no significant difference in pregnancy rates when compared to Cu-IUDs >250 mm^2. And non-hormonal IUDs were associated with a higher likelihood of causing severe menstrual bleeding and pain. We conducted an updated meta-analysis of studies published up to January 13, 2024, assessing the contraceptive efficacy, safety, and effectiveness of Cu-IUDs compared to LNG-IUDs.

Added value of this study

This meta-analysis included 14,673 women of reproductive age using intrauterine contraceptive devices. And provides a robust and comprehensive review of the existing primary evidence, offering insights into the contraceptive effectiveness and potential side effects of IUDs.

Implications of all the available evidence

Currently, the two most commonly used types of IUDs are the LNG (52 mg) IUD and the copper (380 mm^2) IUD. Compared to the copper (380 mm^2) IUD, the LNG-IUD had a lower risk of discontinuation due to dysmenorrhea and increased bleeding, but a higher risk of discontinuation due to bleeding issues and amenorrhea and were associated with a lower risk of pregnancy and adverse effects. While our findings reveal statistical significance, it is imperative to exercise caution when extrapolating their clinical significance and for healthcare providers to provide comprehensive counseling on the diverse attributes of IUDs.

Introduction

In the United States, the unintended pregnancy rate is approximately 45%.[1] Long-acting reversible contraception is an effective option for preventing pregnancy. Intrauterine contraception, including copper intrauterine devices (Cu-IUDs) and levonorgestrel intrauterine devices (LNG-IUDs), is a reversible method with the longest duration of effectiveness. It is suitable for women of reproductive age, including adolescents, parous women, and nulliparous women.[2] Globally, an estimated 19.4% of women of reproductive age use intrauterine contraception.[3] Currently, there are four types of intrauterine devices (IUDs) available in the United States: one copper (380 mm^2) IUD and three LNG (13.5 mg, 19.5 mg, or 52 mg) IUDs.[2] Other regions also include copper IUDs with different copper wire surface areas (220 mm^2 and 200 mm^2).[4,5]

According to the *2024 U.S. Selective Practice Recommendations for Contraceptive Use*, the medical eligibility criteria (MEC) for IUD use falls between U.S. MEC 1 and 2, with cervical cancer and purulent cervicitis being contraindications for use.[2] Currently, guidelines recommend two types of IUDs as preferred methods.[2,6,7] In 2004, a systematic analysis of randomized controlled trials (RCTs) showed that LNG-IUDs had similar unintended pregnancy rates compared to Cu-IUDs >250 mm^2 but were superior to Cu-IUDs ≤250 mm^2.[8] Differences between these two types of devices still exist, but recent evidence is lacking. Recent RCTs indicated that the LNG (52 mg) IUD was more effective than the Cu (380 mm^2 and 220 mm^2) IUDs in preventing unintended pregnancies.[5,9] However, differences between these devices persist. Additionally, almost all relevant studies reported adverse effects associated with IUDs, but there was no consensus on issues such as expulsion and bleeding. A comprehensive answer on which type of IUD provides better contraceptive efficacy and fewer side effects is still lacking.

Recently, several RCTs comparing LNG-IUD with Cu-IUD have been published, but they have not yet been included in the latest guidelines or meta-analyses.[5,9–20] To provide better guidance for clinical practice, we conducted a comprehensive meta-analysis comparing the efficacy and safety of LNG-IUDs and Cu-IUDs.

Methods

This meta-analysis was conducted in accordance with the PRISMA 2020 statement.[21] The study protocol was registered on PROSPERO (CRD42024496400).

Search strategy and selection process

A systematic literature search was conducted across major academic databases, including EMBASE, PubMed, Web of Science, and the Cochrane Library, covering the period from inception to January 13, 2024. The search strategy had been elucidated in the Supplement. Our eligibility assessment also included references to relevant meta-analyses and systematic reviews obtained throughout the search process. After importing the retrieved articles into Endnote ×20, duplicate records were first removed. Then, two reviewers independently screened the titles and

abstracts to identify potential studies that might meet the inclusion criteria. In cases of disagreement, a third reviewer was consulted. The pre-defined inclusion criteria were randomized controlled trials comparing any dosage of LNG-IUDs with any surface area of Cu-IUDs and reporting the outcomes of interest. The two reviewers removed duplicate articles and screened the remaining ones at the title and abstract levels, followed by full-text screening. Any discrepancies were resolved through discussion first, and if no consensus was reached, a senior reviewer was consulted for resolution.

Data extraction

The information extracted included title, author, year of publication, experimental design, sample size, participant characteristics, duration of follow-up, and outcome metrics. The outcomes of interest included pregnancy, continuation, reasons for discontinuation, bleeding issues, pain, pelvic pain, dysmenorrhea, pelvic inflammatory disease (PID), hormonal side effects, abdominal bloating, and satisfaction. The focus on pregnancy included intrauterine pregnancy, ectopic pregnancy and ectopic pregnancies rate of total pregnancy. Reasons for discontinuation included side effects, expulsion, personal reasons, and planned pregnancy. Bleeding issues mainly involved amenorrhea, increased bleeding (heavy menstrual bleeding, prolonged bleeding), decreased bleeding (hypomenorrhea, mild bleeding, infrequent bleeding, spotting, irregular bleeding). Hormonal side effects included ovarian cysts, emotional disturbances, headaches, acne, and weight changes. We categorized Cu-IUDs by the surface area of the copper wire into two groups: those with ≤ 250 mm^2 and those with >250 mm^2. Similarly, we classified the LNG-IUDs as a single group based on the dosage of levonorgestrel: 52 mg. We then conducted comparative analyses. In case of data loss, the corresponding author would be contacted to request the original information as far as possible; if this was unsuccessful, the desired values would be extracted from graphs using a plot digitizer.

Quality assessment

For the included randomized controlled trials, two authors conducted an independent assessment of the risk of bias (selection, performance, detection, attrition, and reporting bias) of included trials using the Cochrane risk of bias tool. Where consensus could not be reached through discussion, a senior reviewer was consulted.

Statistics

The meta-analysis was conducted using RevMan 5.3 and R 4.4.1. Due to the heterogeneity of interventions and demographics, a random effects model was used for analysis. The dichotomous outcomes were evaluated by risk ratio (RR) with a 95% confidence interval (CI). The Mantel-Haenszel method was employed to compute the pooled RR. A significance level of $P < 0.05$ was deemed statistically significant. The statistical heterogeneity between studies was evaluated by I^2 statistics, where I^2 >50% was considered significant for heterogeneity. Egger's test and Begg's test were performed to examine publication bias, and applied trim-and-fill method to test for robustness. Sensitivity analysis examined the robustness of results using leave-one-out method. Sensitivity analysis of the primary outcome was conducted by excluding studies with high risk of bias. Detecting the source of heterogeneity in the main results through subgroup analysis. For the meta-analysis of pregnancy rates, we used a logistic random-intercept model. The model parameters were back-transformed, and the results were expressed as the percentage of patients who experienced contraceptive failure (pregnancy rate).

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation system (GRADE) was used to rate the quality of evidence for each outcome.[22] The overall certainty of evidence for each of the five GRADE domains was categorized into four levels: high, moderate, low, and very low.

Ethics

This analysis used data that had been collected, analyzed, and published in previous studies, all of which had undergone ethical review and approval and were conducted with patient knowledge and consent. The data were fully anonymized. Since the existing data was completely anonymous and could not be traced back to identifiable individuals by the researchers, an ethical review was not required.

Role of the funding source

The study's funders had no role in the study design, data collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Results

Search results

The PRISMA flowchart (Fig. 1) illustrates a complete flow diagram of our literature search and study selection process. A total of 973 records were retrieved from the preliminary database search. After eliminating duplicates, 766 articles remained. Then, by examining titles and abstracts, 724 entries were excluded. The remaining 42 articles were reviewed in full text, and 22 were further excluded (a list of excluded studies is available in the Supplement). Eventually, our meta-analysis included a total of 20 eligible studies.[4,5,9–20,23–28]

Study characteristics

Details of the study, participant characteristics, and results are provided in Table 1. Across the 20 included

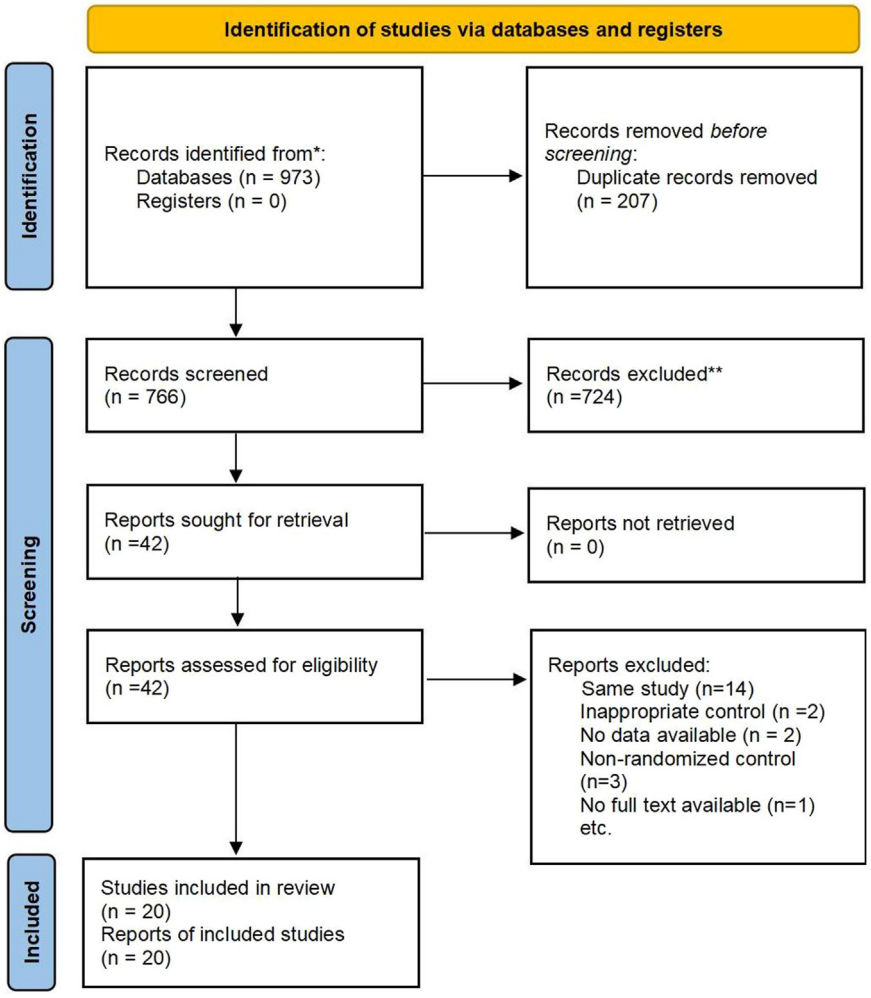

Fig. 1: PRISMA flowchart of study selection.

randomized controlled trials, there were a total of 14,673 participants (7475 in the LNG-IUDs group and 7198 in the Cu-IUDs group), with sample sizes ranging from 11 to 1922 individuals. The mean age of participants ranged from 17.9 years to 47.4 years. Among these, the comparison between Cu (380 mm^2) IUD and LNG (52 mg) IUD is the most common. Out of 20 studies, 13 were flagged for high bias risk in at least one domain (see Supplementary Material). Among these 13 studies, 12 lacked blinding of participants and/or personnel, introducing a high risk of performance and detection bias.[4,5,10–12,17,19,23,24,26–28] Furthermore, 2 of these 13 studies did not detail their randomization methods, potentially indicating selection bias[11,23] (Supplemental File).

Pregnancy outcomes

Ten studies reported pregnancy outcomes, and the pooled results showed that the risk of pregnancy with LNG-IUDs was lower than with Cu-IUDs (Risk Ratio 0.22, 95% confidence interval 0.12–0.39) (Fig. 2). The pregnancy rate was 2.0% for Cu-IUDs and 0.3% for LNG-IUDs (Supplementary Files). Comparisons between the LNG (52 mg) IUD and Cu-IUDs >250 mm^2 (RR 0.26, 95% CI 0.13–0.51) and ≤250 mm^2 (RR 0.12, 95% CI 0.02–0.89) also indicated that the LNG (52 mg) IUD had a lower pregnancy risk. The pregnancy rate is 1.2% for Cu-IUDs >250 mm^2 and 0.3% for LNG (52 mg) IUD. Further meta-analysis of six studies revealed that the risk of intrauterine pregnancy with LNG-IUDs was significantly lower compared to Cu-IUDs (RR 0.30, 95% CI 0.12–0.77) (Fig. 3). Additionally, combined results from four studies showed that the risk of ectopic pregnancy with LNG-IUDs was lower (RR 0.12, 95% CI 0.03–0.47) (Fig. 3). The incidence of ectopic pregnancy per 100 individuals was 0.01% for LNG-IUDs and 0.3% for Cu-IUDs (Supplementary Files). However, there was no statistically significant difference between LNG-IUDs and Cu-IUDs regarding the occurrence rate of ectopic

Source	Region	Registration number	Insertion time	Total follow-up time (mo)	Sample size			Type of contraceptive device		Age (SD)	
					LNG-IUDs	Cu-IUDs	Total	LNG-IUDs; dose (mg)	Cu-IUDs; surface area (mm^2)	LNG-IUDs	Cu-IUDs
Andersson et al. (1994)	Europe	NA	Within 10 days of the start of menstruation or early miscarriage	60	1821	937	2758	46	200	30.3	30.3
Anjos et al. (2023)	South America	REBEC No. 11732	Insertion within the first 7 days of the menstrual cycle	12	212	106	318	52; 19.5	380	17.9 ± 1.4	17.9 ± 1.2
Baveja et al. (1989)	Asia	NA	Within 10 days after the last menstrual period or during surgical abortion at the hospital	36	475	1430	1905	52	380; 220; 200	26.0 ± 4.3	25.9 ± 4.1
Bilgehan et al. (2015)	Europe	NA	Immediate insertion post-abortion	6	50	50	100	52	380	29.27 ± 5.04	30.82 ± 5.09
Godfrey et al. (2010)	North America	NA	Within the first 5 days of the menstrual cycle	6	12	11	23	52	380	NA	NA
Heikkilä et al. (1982)	Europe	NA	6 weeks postpartum	12	70	40	110	56; NA	200	27.4 ± 3.1	25.8 ± 6.1
Ju et al. (2017)	Asia	NA	Immediate insertion post-abortion	12	56	60	116	52	220	25.34 ± 4.53	25.56 ± 4.28
Kakaire et al. (2015)	Africa	PACTR 201308000561212	NA	12	354	349	703	52	380	29.5 ± 6.3	30.4 ± 6.2
Kapur et al. (2008)	NA	NA	Insertion between day 1 and day 7 of menstruation	12	70	70	140	NA	380	NA	NA
Mahgoub et al. (1982)	Africa	NA	On the first day of menstruation	36	200	100	300	NA; 18.25	200	NA	NA
Marangoni et al. (2021)	South America	REBEC; No. RBR-67H649	Insertion after vaginal delivery or cesarean section	12	70	70	140	52	380	NA	NA
Nilsson et al. (1983)	Europe、North America	NA	NA	20	227	157	384	48	200	NA	NA
Perelló-Capó et al. (2023)	Europe	EudraCT: 2015-004956-23	NA	36	55	51	106	13.5	380	32.2 ± 7.3	32.9 ± 6.2
Ramazanzadeh et al. (2012)	Europe	IRCT138903013881N2	NA	6	80	80	160	52	380	4.25 ± 26.54	4.3 ± 26.49
Rowe et al. (2016)	NA	NA	NA	84	1922	1914	3836	52	380	29.8 ± 5.12	29.9 ± 4.95
Shaamash et al. (2005)	Africa	NA	6–8 weeks postpartum	12	163	157	320	52	380	46.9 ± 6.9	47.4 ± 7.7
Shain et al. (1989)	Europe	NA	NA	12	86	69	155	NA	200	NA	NA
Sivin et al. (1991)	Europe	NA	NA	60	1124	1121	2245	60	380	26.6 ± 0.1	26.7 ± 0.1
Todd et al. (2020)	Africa	NCT01721798	NA	24	101	98	199	52	380	31.4 ± 4.9	31.4 ± 4.6
Turok et al. (2021)	North America	NCT02175030	Emergency contraception required within 120 h after unprotected intercourse	1	327	328	655	52	380	24.0 ± 4.9	23.9 ± 4.6

NA, not available; LNG, levonorgestrel; IUS, levonorgestrel intrauterine system; IUD, intrauterine device.

Table 1: **Characteristics of included randomized controlled trials.**

pregnancy within the total number of pregnancies. No significant differences in intrauterine pregnancy or ectopic pregnancy rates were found when comparing the LNG (52 mg) IUD with Cu-IUDs >250 mm^2 (Fig. 3).

Reasons for discontinuation

Regarding expulsion, there was no statistically significant difference between LNG-IUDs and Cu-IUDs (Fig. 3). The expulsion rate was 6.1% for Cu-IUDs and 4.9% for LNG-IUDs (Supplementary Files). Further analysis of discontinuation due to side effects showed no statistically significant difference between the two (Fig. 3). Pooled results from eight studies indicated that the risk of amenorrhea with LNG-IUDs was lower compared to Cu-IUDs (RR 21.02, 95% CI 8.83–50.00) (Fig. 3). Summarized results from nine studies revealed that the risk of increased bleeding was lower with LNG-IUDs compared to Cu-IUDs (RR 0.49, 95% CI

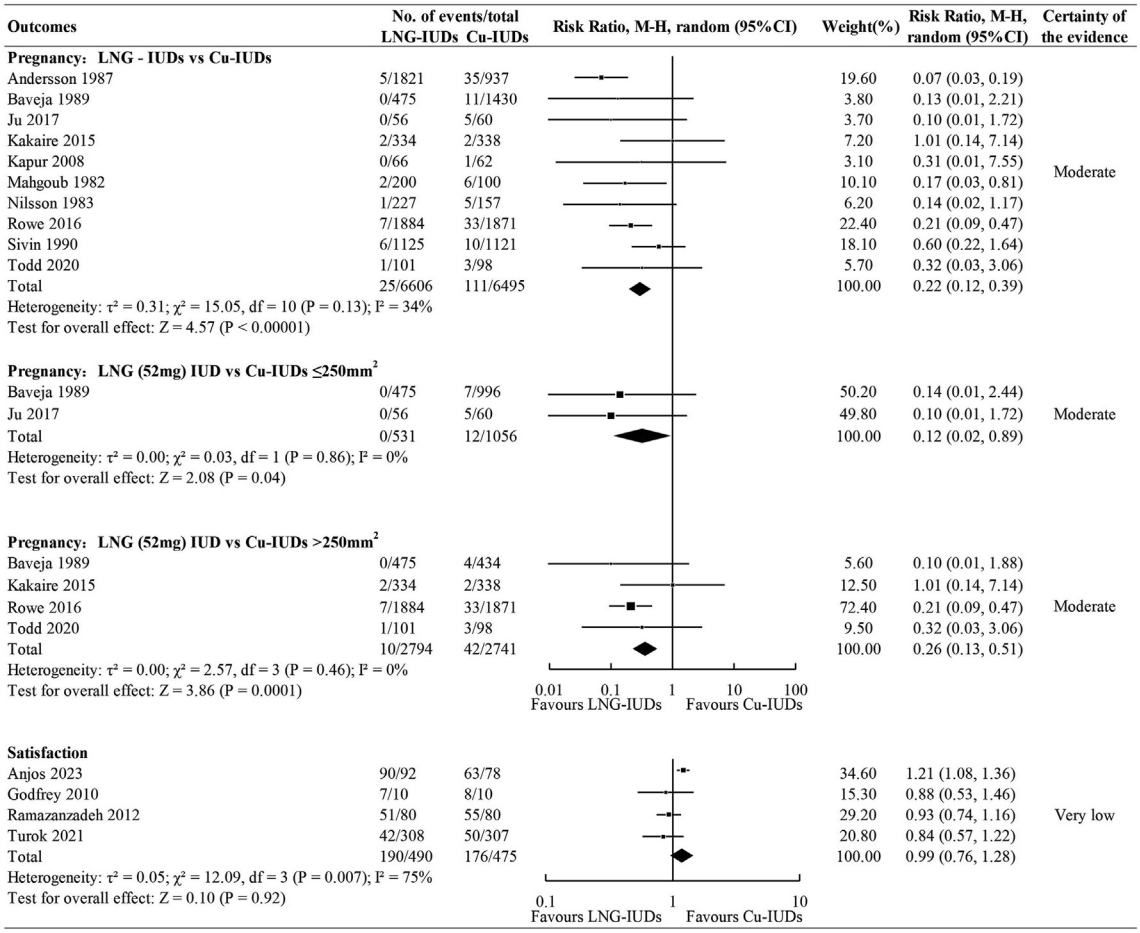

Fig. 2: A forest plot comparing intrauterine pregnancy, ectopic pregnancy, and overall pregnancy rates between LNG-IUDs and Cu-IUDs. Data obtained from RCTs using random effect meta-analysis and expressed as risk ratio. Cu-IUDs, copper intrauterine devices; LNG-IUDs, levonorgestrel intrauterine devices; CI, confidence interval; M-H, Mantel-Haenszel.

0.28–0.58). However, the pooled analysis showed that the risk of hormonal side effects with LNG-IUDs was significantly higher than with Cu-IUDs (RR 3.73, 95% CI 1.32–10.53). Additionally, combined results from four studies showed a higher risk of headache with LNG-IUDs (RR 5.90, 95% CI 2.04–17.00), and pooled results from two studies indicated a higher risk of acne with LNG-IUDs (RR 5.96, 95% CI 2.27–15.62) (Fig. 3). In the comparison between LNG (52 mg) IUD and Cu-IUDs >250 mm^2, the risk of discontinuation due to bleeding was significantly higher for Cu-IUDs >250 mm^2 compared to LNG (52 mg) IUD (RR 2.83, 95% CI 2.47–3.35). Additionally, the risk of discontinuation due to reduced bleeding was significantly higher with LNG (52 mg) IUD than with Cu-IUDs >250 mm^2 (RR 3.20, 95% CI 2.37–4.32), while the risk of discontinuation due to increased bleeding was significantly lower with LNG (52 mg) IUD compared to Cu-IUDs >250 mm^2 (RR 0.68, 95% CI 0.55–0.85) (Fig. 3).

In comparisons between LNG-IUDs and Cu-IUDs, no significant differences were found for personal reasons, planned pregnancy, bleeding issues, decreased bleeding, frequent/irregular bleeding, heavy menstrual bleeding, prolonged bleeding duration, spotting, pain, dysmenorrhea, emotional disturbances, weight changes, and PID. When comparing LNG (52 mg) IUD with Cu-IUDs >250 mm^2, there were no significant differences in side effects leading to discontinuation, personal reasons, planned pregnancy, amenorrhea, heavy menstrual bleeding, prolonged bleeding duration, pain, hormonal side effects, and PID (Fig. 3).

There were no observed differences in expulsion between LNG (52 mg) IUD and Cu-IUDs ≤250 mm^2 (Fig. 3).

Continuation and non-discontinuation related side effects

In comparisons between different types of LNG-IUDs and Cu-IUDs (LNG-IUDs versus Cu-IUDs, LNG

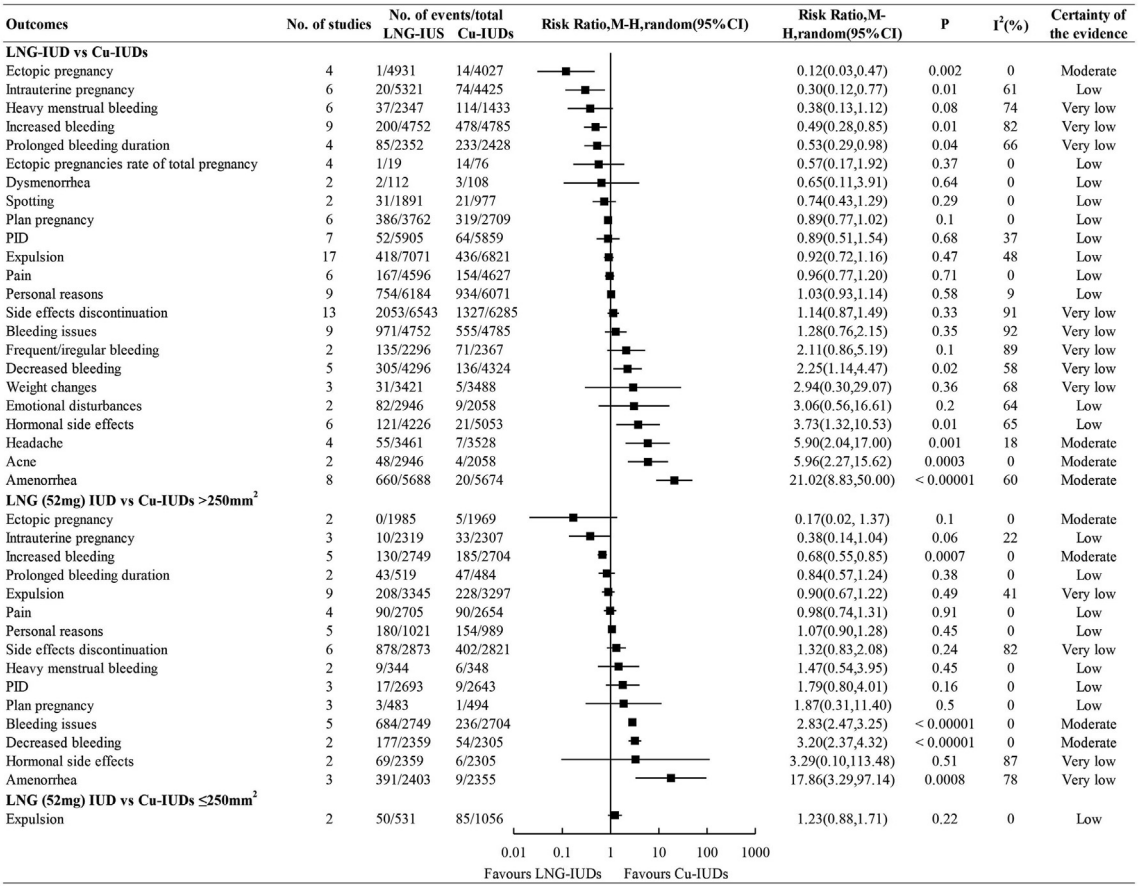

Fig. 3: A forest plot comparing the reasons for discontinuation between LNG-IUDs and Cu-IUDs. Grouping: Cu-IUDs are classified into two categories based on the surface area of the copper wire: ≤250 mm^2 and >250 mm^2. LNG-IUDs are grouped as a single category based on the dosage of levonorgestrel: 52 mg. Data obtained from RCTs using random effect meta-analysis and expressed as risk ratio. Cu-IUDs, copper intrauterine devices; LNG-IUDs, levonorgestrel intrauterine devices; CI, confidence interval; M-H, Mantel-Haenszel.

(52 mg) IUD versus Cu-IUDs >250 mm^2), there were no significant differences in continuation (Fig. 4). The pooled results showed that, compared to Cu-IUDs, LNG-IUDs were associated with a higher risk of amenorrhea (RR 3.57, 95% CI 1.45–8.79) and hypomenorrhea (RR 2.87, 95% CI 1.20–6.81), but a lower risk of increased bleeding (RR 0.42, 95% CI 0.25–0.7), heavy menstrual bleeding (RR 0.41, 95% CI 0.22–0.75), and dysmenorrhea (RR 0.41, 95% CI 0.34–0.48). For other reasons, there were no statistically significant differences between LNG-IUDs and Cu-IUDs in terms of bleeding issues, decreased bleeding, prolonged bleeding duration, irregular bleeding, pelvic pain, pain, hormonal side effects, ovarian cysts, headache, acne, weight changes, emotional disturbances, PID, and abdominal bloating (Fig. 4).

In the comparison between LNG (52 mg) IUD and Cu-IUDs >250 mm^2, the risk of amenorrhea (RR 5.92, 95% CI 2.81–12.49) and decreased bleeding (RR 1.88, 95% CI 1.12–3.14) was higher with LNG (52 mg) IUD, while the risk of increased bleeding (RR 0.46, 95% CI 0.25–0.83), heavy menstrual bleeding (RR 0.44, 95% CI 0.21–0.91), and dysmenorrhea (RR 0.42, 95% CI 0.34–0.53) is higher with Cu-IUDs >250 mm^2. No significant differences were found in bleeding issues, pelvic pain, pain, hormonal side effects, ovarian cysts, headache, acne, weight changes, and abdominal bloating (Fig. 4).

Satisfaction

Five studies reported the outcome of satisfaction, and the pooled outcome showed that there was no statistically significant difference between Cu-IUDs and LNG-IUDs (Fig. 2).

Publication bias and sensitivity analysis

A funnel plot, Egger's test, and Begg's test were performed to assess publication bias, and the results indicated no significant bias. However, continuation (Egger = 0.0373) and adverse event-related discontinuation

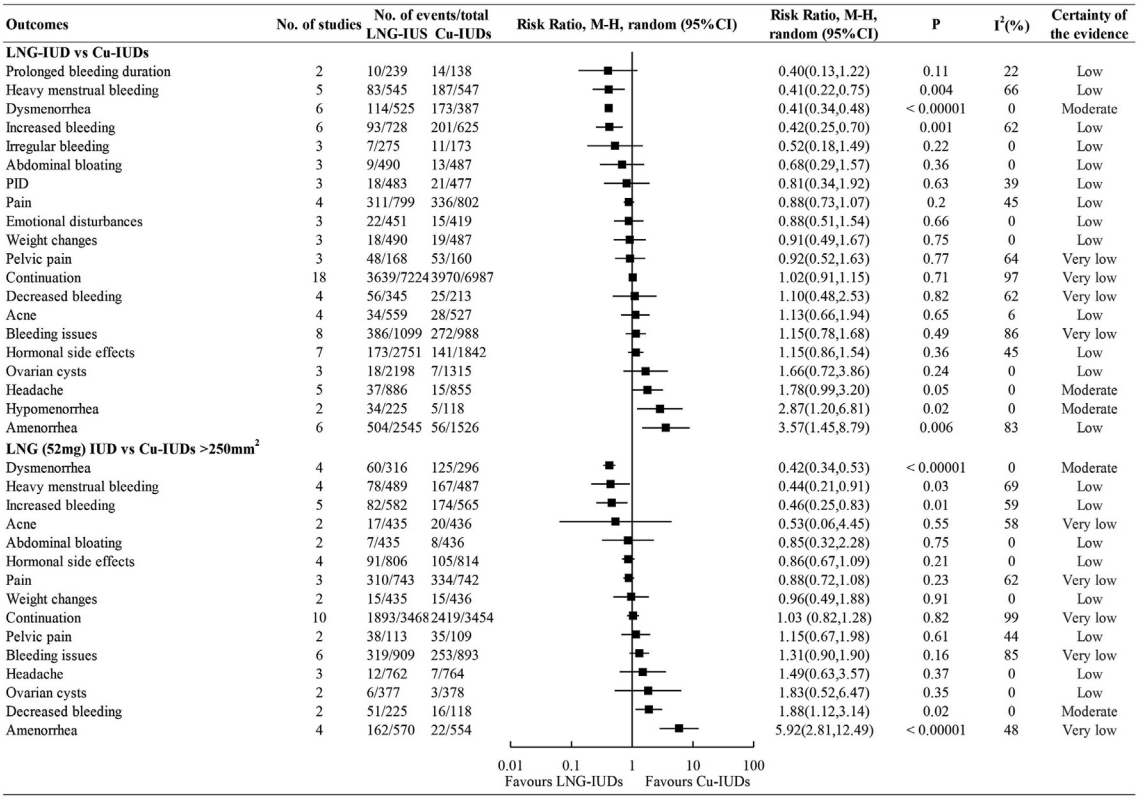

Fig. 4: A forest plot comparing the reasons for non-discontinuation between LNG-IUDs and Cu-IUDs. Data obtained from RCTs using random effect meta-analysis and expressed as risk ratio. Cu-IUDs, copper intrauterine devices; LNG-IUDs, levonorgestrel intrauterine devices; CI, confidence interval; M-H, Mantel-Haenszel.

(Egger = 0.0028) in comparing LNG-IUDs with Cu-IUDs, as well as continuation (Egger = 0.0481) and adverse event-related discontinuation (Egger = 0) in comparing the LNG (52 mg) IUD with Cu-IUDs >250 mm^2, suggested the potential for publication bias. Nonetheless, the trim and fill analysis confirmed the robustness of the results, leading to the conclusion of no publication bias (Supplementary Files).

Sensitivity analysis indicated that the reasons for discontinuation when comparing LNG-IUDs with Cu-IUDs included pregnancy, ectopic pregnancy, ectopic pregnancy rate of total pregnancies, expulsion, side effects leading to discontinuation, personal reasons, planned pregnancy, amenorrhea, increased bleeding, pain, weight changes, and PID. Additionally, reasons associated with continued use included bleeding issues, increased bleeding, heavy menstrual bleeding, irregular bleeding, dysmenorrhea, pelvic pain, hormonal side effects, ovarian cysts, acne, weight changes, emotional disturbances, PID, abdominal bloating, and satisfaction. These factors showed consistent associations in the analysis, indicating the robustness of the study results. In the analysis comparing LNG (52 mg) IUD and Cu-IUDs >250 mm^2, the associations for expulsion, personal reasons, planned pregnancy, bleeding issues, decreased bleeding, increased bleeding, pain, and PID, as well as non-discontinuation related reasons such as bleeding issues, amenorrhea, dysmenorrhea, hormonal side effects, and headache, were also consistent, further indicating the robustness of the findings. Even in cases where the I^2 >50%, the robustness of these results suggested that they were reliable (Supplementary Files).

We performed a sensitivity analysis on the primary outcomes by excluding studies judged to have a high risk of overall bias. When studies with a high risk of bias were excluded from the analysis, LNG-IUDs remained superior to copper IUDs in preventing pregnancy. (RR 0.31, 95% CI 0.14–0.71; P = 0.005; I^2 = 15%) (Supplementary Files).

Subgroup analyses

Subgroup analyses were conducted on pregnancy based on follow-up duration, publication date, location, age, insertion timing, type of intrauterine device, and sample size. In the initial analysis, the pregnancy risk associated with LNG-IUDs was statistically significantly lower than that of the Cu-IUDs. LNG-IUDs also showed consistent results in most subgroups (publication date, age, sample

size, and type of intrauterine device). However, no statistically significant differences were found among the subgroups with follow-up durations exceeding three years, Europe, and postpartum insertion, but their trends aligned with the initial analysis. Tests for subgroup differences indicated that none of the subgroup effects were statistically significant, suggesting consistency in the overall effect. However, the limited number of studies included in these subgroups warrants caution when interpreting these results (Supplementary Files).

Certainty of evidence

The certainty of all outcomes ranged from moderate to very low, due to downgrades in evidence quality caused by the inclusion of numerous studies with high risk of bias, as well as downgrades related to inconsistency and imprecision (Supplementary Files). We excluded studies with a high risk of overall bias from the primary outcomes analysis. After excluding these high-risk-of-bias studies, LNG-IUDs were superior to Cu-IUDs in preventing pregnancy, and the certainty of evidence was high (Supplementary Files).

Discussion

This meta-analysis included 14,673 patients who used intrauterine contraceptives. When studies with a high risk of bias were excluded from the analysis, LNG-IUDs remained superior to Cu-IUDs in preventing pregnancy. The certainty of evidence was high, while other evidence had a certainty ranging from moderate to very low. The results suggested that, compared to Cu-IUDs, LNG-IUDs were associated with lower risks of pregnancy, ectopic pregnancy, and adverse outcomes, but a higher risk of amenorrhea. When comparing LNG (52 mg) IUD with Cu-IUDs >250 mm^2, LNG-IUDs were associated with a lower risk of discontinuation due to increased bleeding and a lower risk of dysmenorrhea, but a higher risk of discontinuation due to bleeding issues and amenorrhea. Additionally, there were no significant differences in satisfaction, side effects leading to discontinuation, expulsion, and other adverse outcomes between the two types. Our study was the most comprehensive to date in terms of study inclusion, data volume, and data sources. We evaluated all analyzable outcomes using a risk-based approach and employed the GRADE framework to assess evidence quality, focusing on the absolute effects of IUDs. Additionally, the reliability of our findings was supported by their robustness, absence of publication bias, and low heterogeneity in the primary outcomes. Current guidelines recommend IUDs as a first-line contraceptive method, but there are differences in the choice of specific IUD types. Our findings can inform future investigations for the revisions of guidelines.

Currently, only one meta-analysis had compared LNG-IUDs and Cu-IUDs, but that review incorporated merely four pertinent RCTs.[8] Our meta-analysis included all relevant RCTs to date and provided a comprehensive synthesis of data on the contraceptive efficacy of Cu-IUDs and LNG-IUDs. Additionally, we focused on pregnancy as the primary outcome, examining intrauterine pregnancy, ectopic pregnancy, and the proportion of ectopic pregnancies among total pregnancies. By including a larger number of studies, we mitigated the potential impact of insufficient sample size on the stability of the meta-analysis results. We also conducted subgroup analyses to explore sources of heterogeneity. The results, whether in combined analysis or separate comparisons, showed a trend of LNG-IUDs indicating small but statistically superior contraceptive efficacy compared to copper IUDs, despite the overall lower pregnancy rates (Cu-IUDs 2.0% and LNG-IUDs 0.3%). Our findings also indicated that Cu-IUDs had a higher risk of ectopic pregnancy compared to LNG-IUDs. However, among the population with contraceptive failure, there is no significant difference in the risk of ectopic pregnancies between the two. Whether considering the overall trend or specifically comparing LNG (52 mg) IUD with Cu (380 mm^2) IUD, LNG-IUDs show a higher risk of amenorrhea. Currently, menstrual suppression caused by LNG-IUDs is widely regarded as a therapeutic benefit, but amenorrhea is less acceptable to many individuals and a cause for discontinuation.[29] Rowe et al.'s study[9] indicates that the discontinuation rate due to amenorrhea is nearly twice as high in Chinese centers compared to non-Chinese centers (31.0 versus 15.6 per 100). Among the included studies, twelve reported[4,9,11,14–16,19,20,24–26,28] amenorrhea as a side effect, predominantly from Europe and Asia. These geographical and cultural differences imply varying attitudes toward amenorrhea. Currently, some studies report that LNG-IUDs with lower doses result in lower rates of amenorrhea, which might be a better choice for patients sensitive to amenorrhea.[30] However, only three studies[19,20,23] have discussed LNG-IUDs with dosages below 20 mg, limiting our discussion on lower-dosage LNG-IUDs and necessitating further research to explore this finding. Additionally, the abnormal bleeding caused by IUDs tends to decrease with continued use of the IUD.[2] In comparisons between Cu-IUDs and LNG-IUDs, Cu-IUDs were associated with higher rates of discontinuation due to increased bleeding and dysmenorrhea, consistent with findings from comparisons of LNG (52 mg) IUD with Cu (380 mm^2) IUD. Conversely, LNG-IUDs showed higher rates of discontinuation due to reduced bleeding, but this conclusion should be approached cautiously due to the robustness of the findings and the fact that only two studies were included in the comparison between LNG (52 mg) IUD and Cu (380 mm^2) IUD. Further high-quality RCTs are needed to validate these conclusions and provide stronger evidence for future clinical practice.

Almost all of the included studies reported the risk of expulsion, with expulsion being considered a discontinuation in the studies. The overall expulsion rate over five years was low (4.9% for LNG-IUDs and 6.1% for Cu-IUDs), and no significant differences were found in comparisons among the various LNG IUDs and Cu-IUDs. One meta-analysis[31] indicated that LNG-IUDs had a higher risk of expulsion compared to copper IUDs. The expulsion rates of IUDs vary depending on the placement time, type, and delivery method. Most studies included in our review did not reporte precise placement times or delivery methods, highlighting the need for further research to investigate how placement time and delivery methods affect the expulsion rates of these contraceptive devices.

Turok et al.[18] suggested that the LNG (52 mg) IUD is not inferior to the Cu (380 mm^2) IUD for emergency contraception. However, their study's sample size was insufficient to draw a conclusion of non-inferiority.[32] Due to significant differences in the timing of IUD insertion following unprotected intercourse in their study compared to other studies, we did not include pregnancy outcomes for a meta-analysis. The lack of available literature made it challenging to explore the differences between LNG-IUDs and Cu-IUDs in emergency contraception. Further research is needed to investigate the effectiveness of LNG-IUDs for emergency contraception and to provide patients with more options for emergency contraceptive methods.

Finally, to our knowledge, there has not been a meta-analysis that thoroughly examines the balance of potential benefits and harms of the two types of IUDs regarding menstrual disorders and hormonal side effects, nor has there been an analysis of patient satisfaction with IUDs. Although our results demonstrate significant statistical findings, caution must be exercised when interpreting their clinical significance. According to traditional clinical statistics, a RR value below 0.5 or above 2 is typically considered clinically significant.[33] In our study, most conclusions met this criterion, suggesting clinical differences between the two types of IUDs. However, the RR value alone is not absolute and should be evaluated in the context of individual patient needs and the real-world clinical setting. Therefore, while our findings indicated clinical significance based on RR values, this does not imply a clear clinical superiority of one IUD over the other. Ultimately, the decision should be based on the patient's personal needs and made in consultation with their healthcare team.

This meta-analysis has several implications for clinical guidelines and the use of IUDs. The *2024 U.S. Selective Practice Recommendations for Contraceptive Use* states that if a woman is reasonably confirmed not to be pregnant, a health care provider can insert an IUD at any time.[2] Similarly, Canadian contraceptive guidelines recommend that health professionals should consider IUDs as a primary contraceptive method for both nulliparous and parous women.[6] For women seeking an IUD and experiencing heavy menstrual bleeding and/or dysmenorrhea, providers are advised to consider the LNG (52 mg) IUD rather than other IUDs options. Additionally, the latest clinical practice guidelines from the French National College of Obstetricians and Gynecologists (CNGOF)[7] suggest that LNG-IUDs are the most effective treatment for improving the quality of life in women with heavy menstrual bleeding, with fewer complications compared to Cu-IUDs. Furthermore, the use of LNG-IUDs significantly reduces dysmenorrhea risk compared to Cu-IUDs. Given the observed differences between LNG-IUDs and Cu-IUDs, there is a need to reassess current guidelines and consider revisions to better reflect the evidence provided by this study.

Despite the benefits, the global use of IUDs remains uneven.[34] In a few countries, including China and much of Central Asia, IUDs accounted for over half of all contraceptive methods. In North Africa and the Middle East, IUD use comprised about one-quarter of all contraceptive methods, while in some regions of Europe, this proportion is around one-fifth. However, in the United States, the use of IUDs remained relatively low. In 2015–2017, 7.9% of women aged 15–49 were using IUDs, which increased to 8.4% in 2017–2019.[35] Both LNG-IUDs and Cu-IUDs are highly effective contraceptive methods, although they differ in effectiveness and side effects. The increasing use of IUDs faces potential barriers, with cost being a significant factor. For instance, in the United States, in 2014, the average insertion cost of a LNG (13.5 mg) IUD was $931, while the average cost of a LNG (52 mg) IUDs was $1107, and Cu-IUDs averaged $897.[36] Reducing the costs associated with IUDs is crucial to making them a viable option in low-income countries.

Our analysis had several limitations. First, there were significant differences in the definitions and diagnoses of some outcomes. For instance, assuming "complete" expulsion of intrauterine devices may have overestimated expulsion rates. Second, combining all types of IUDs, including experimental ones, in the analysis might introduce confusion, potentially limiting the generalizability of the reported results for IUDs. Additionally, there was limited research comparing LNG-IUDs with 13.5 mg and 19.5 mg levonorgestrel doses to Cu-IUDs with different surface areas, making it difficult to explore the differences between low-dose LNG-IUDs and Cu-IUDs. This limited our ability to make conclusive statements on these aspects, and more high-quality studies are needed for a more comprehensive data synthesis in the future. Third, incomplete reporting in some studies, including device types, insertion times, and participant characteristics, hindered a thorough analysis of heterogeneity sources. Fourth, few studies reported non-termination side effects, potentially leading to underestimation. Fifth, we were unable to adjust for potential confounders that

were inconsistently reported, such as provider training and experience, ultrasound use, and insertion techniques. Sixth, the limited number of included studies restricted our exploration of the highly heterogeneous results. Lastly, in our study, 60% of the included research had follow-up periods of one year or less, which is insufficient to comprehensively assess the long-term efficacy and safety of intrauterine devices (IUDs). Certain adverse reactions may only become apparent with prolonged use. Therefore, our findings provide limited evidence for comparing the long-term effects of these two types of IUDs, and we recommended cautious interpretation of these results in clinical practice. We emphasized the need for more long-term follow-up studies to thoroughly evaluate the efficacy and safety of both types of IUDs, thereby addressing the existing gaps in the current literature.

Contributors

PL and SG developed the initial idea for the study, drafted the manuscript, and SG is the guarantor. PL, JM, YX, YW, and SG drafted the initial study protocol. PL and JM conducted the screening, extraction, and risk of bias assessment. PL and JM performed the statistical analyses. PL and SG provided supervision and mentorship. PL and JM had access to and verified the underlying data. All authors provided critical revision of the manuscript for important intellectual content and gave approval of the submission of the manuscript for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The full dataset used in this study is available for viewing and replication in additional files accompanying this article (see Supplement).

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102926.

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