Title: Short term effects of levonorgestrel-releasing intrauterine systems: a systematic review with meta-analysis

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Running title: Systematic review with meta-analysis of short term effects of LNG-IUS

Abstract

Background: The levonorgestrel intrauterine systems (LNG-IUS) is widely used, but few studies report incidence rates of side-effects of LNG-IUS.

Objectives: The purpose of this study was to investigate short term side effects of LNG-IUS and to compare the side effects at different dosages of LNG-IUS's.

Search strategy: We searched electronic databases (MEDLINE, Embase, Cochrane) for RCT's and observational studies between January 1970 and April 2019 published in English.

Selection criteria: Studies including women seeking contraception and receiving a LNG-IUS, compared to either women without hormonal contraception or a different dosage of a LNG-IUS.

Data Collection and analysis: We evaluated randomized controlled trials with the Cochrane Risk of Bias tool and observational studies with ROBINS-I. For outcomes with data from at least two studies, meta-analysis was conducted using RevMan (version 5.3). The quality of evidence was assessed using the GRADE.

Main results: We found an increase in risk of nervousness, depression, ovarian cysts and of amenorrhea. One study compared two different LNG-IUSs and found a decreased risk of developing ovarian cysts and an uncertain risk of ectopic pregnancies and mood swings in low dose LNG-IUS.

Conclusions: We found that LNG-IUS increases risk of nervousness, depression, ovarian cysts and amenorrhea but the quality of evidence was low and the absolute risk small. Low-dosage LNG-IUS decreases the risk of ovarian cysts compared to high dose. To achieve higher quality of evidence, further studies are needed.

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Keywords: LNG-IUS, LNG-IUD, side-effects, ovarian cysts, amenorrhea, depression, ectopic pregnancies.

Tweetable abstract: Systematic review and meta-analysis showing that LNG-IUS increases risk of depression and amenorrhea and a lower dosage device decreases risks.

Introduction

Only second to female sterilization, intrauterine systems are the most common contraceptives in the world, and the most common reversible contraception(1). There are two types of intrauterine systems: copper-intrauterine systems (cu-IUS) and levonorgestrel-intrauterine systems (LNG-IUS)(2). The LNG-IUS has been available in Europe since 1990 and in the United States since 2000(3). There are two types of LNG-IUS available, differentiated by the amount of levonorgestrel released per day in the first year; high-dose and low-dose. High dose IUSs release about 20 µg of levonorgestrel per day (Mirena, Liletta) and low-dose IUSs release 8-9 µg pr. day (Jaydess/Skyla, Kyleena)(4,5) (table 1).

Levonorgestrel is a synthetic progestogen(4), and the primary effect of LNG-IUS is thickening of the cervical mucus which leads to lack of sperm penetration(6). The effect occurs three-five days after insertion of the LNG-IUS and persists for three-five years depending on the type of LNG-IUS(6,7). Fertility is rapidly restored after removal of an LNG-IUS with 80%–92% of women conceiving within a year(8).

The LNG-IUS is widely used(1), but few studies report incidence rates of side-effects of LNG-IUS. Both the high-dose and low-dose LNG-IUS has proven to be a very efficient method of contraception with very low cumulative pregnancy rates(3,9–11). However, the discontinuation rates for the LNG-IUS are higher than for Cu-IUD due to side-effects as acne, breast tenderness, headaches, development of ovarian cysts and bleeding abnormalities[9-11]. In addition, observational studies have reported an increased risk of breast cancer and depression after use of LNG-IUS(12,13). More information on potential side-effects would be beneficial for clinicians when counselling women, so they together can determine if the benefits outweigh the harm. Furthermore, with different dosages of LNG-IUS, it is important to ensure the safety and efficacy of the low-dose LNG-IUS compared to high-dose LNG-IUS. The aim of this review was to 1) evaluate the incidence of short-term side-effects of LNG-IUS and 2) compare short-term side-effects and risk of ectopic pregnancy between high-dose and low-dose LNG- IUS.

Methods

We conducted a systematic review in accordance with Cochrane methodology(14) and reported it in accordance with the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement(15). The protocol can be found at Prospero (registration number: CRD42019123904).

Eligibility criteria

Studies published in English between January 1970 and March 2019, were deemed eligible. We included Random Clinical Trials (RCTs) and observational studies. The participants in the studies were women desiring contraception.

This review was based on two research questions. For research question 1 we wanted to evaluate the incidence of short-term side effects and we compared LNG-IUS with no hormonal contraception. Primary outcomes for research question 1 were the frequency of ovarian cysts and mood changes. For research question 2 we wished to assess the short-term side effects and the risk of ectopic pregnancies between high-dose and low-dose LNG-IUS. For this research question, the primary outcomes were frequencies of ectopic pregnancies, ovarian cysts and changes in mood. Secondary outcomes investigated for both research questions were amenorrhea, breast discomfort, acne, anovulation, libido, headaches, weight gain and bone mass density. We accepted binary as well as continuous outcomes on scales chosen by the authors. The outcomes had to be present within a year from insertion of the LNG-IUD.

Information sources and search strategy

In February to April 2019 we searched Medline, Embase and Cochrane Central Register of Controlled Trials (Appendix S1). The search strategy clustered terms to describe the design of the study, the intervention with an LNG-IUS and the indication of contraception. The search strategy was initially developed for use in MEDLINE and was then adapted for search in other databases (Appendix S1).

Study selection

Two reviewers (E.H.I, H.T.W.) screened the studies independently. Titles and abstracts of identified publications were screened, and all potentially relevant studies were retrieved for full-text screening. Data extraction were performed independently in an unblinded, standardized manner by two reviewers (E.H.I, H.T.W), and any disagreement in the process was resolved by discussion. If an agreement could not be reached by discussion, a third reviewer (J.B.S) was involved.

Papers only reporting the desired outcomes as reasons for withdrawal and not as a total number of participants experiencing the outcome were excluded. Finally, studies which included women with gynaecological conditions (adenomyosis, endometriosis, fibromas) or hormonal diseases were excluded.

Data extraction and quality assessment

At data extraction, information on setting, study design, number of participants, exclusion criteria, parity, outcomes, length of study and follow-ups were collected. Exposure details for RCTs included the type and model of contraception and the duration of use.

Risk of bias analysis in the included RCTs was performed using the risk of bias tool from Cochrane(16) and ROBINS-I was used on observational studies(17). Risk of bias were reported as low, unclear or high. We did not exclude any studies based on risk of bias.

The quality of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) and was categorized into four levels from very low (+ - - -) to high (++++) (18).

Statistical analysis

We conducted joint meta-analysis including RCTs and observational studies but planned to separate observational studies and RCTs in subgroup analyses. We applied meta-analyses on outcomes with data from at least two studies. These were conducted using RevMan (version 5.3)(19). We used a fixed effect model. Statistical heterogeneity was assessed with the I^2 statistics. As recommended by the Cochrane Library Handbook, we considered an I^2 value of 0-40 % to represent low heterogeneity, 30-60 % substantial heterogeneity and 75-100 % considerable heterogeneity(14). If substantial heterogeneity was found, a random effect model was used to further investigate heterogeneity.

Due to the possible advantage for counselling the number needed to harm (NNH) was calculated for all continuous outcomes.

Results

We identified 2,243 records in the initial search, which was reduced to 1,228 after removal of duplicates with Zotero (Figure 1). After reading the abstracts, we excluded 1,193 records, leaving 33 records eligible for full-text review (Figure 1). Of these, 23 were excluded (Supplementary Table 1), and 10 studies including 9,668 women met our inclusion criteria. The study design and the in- and exclusion criteria varied (Table 2). All studies were RCTs except for one study(20). The authors of this study were contacted but did not respond, and the risk of bias was assessed similarly as in an observational study. The trials had a varying risk of bias (Table 2).

Study participants were mainly recruited from Europe (Table 2). The participants were aged from 18-45 and had very varying parity. The duration of the studies was six months to seven years, and the comparators in all the studies eligible for Research Question 1 were women receiving a Cu-IUS. In the study eligible for Research Question 2, the comparator received a high-dose LNG-IUS (Mirena) and the intervention was low-dose LNG-IUS.

None of the included studies reported on anovulation, libido or bone mineral density.

Research Question 1

Primary outcome: Nervousness

The risk of an increase in nervousness was assessed in three RCT's . A feeling of increased nervousness was reported by participants in questionnaires in all studies taken under review. One study found an increased risk of nervousness(22), while the remaining studies showed an unchanged risk[23,](20). Risk of bias were unclear in one of the RCTs(21) and low in two others(20,22), due to no blinding, or uncertainty about blinding, of participants or outcome assessors. All three studies provided data usable for meta-analysis. The summary relative risk (RR) involving 2,809 women with 196 events was 1.40 (CI 95 % 1.04-1.87) (Figure 2a), with a substantial degree of statistical heterogeneity (I^2 68 %). Because of the substantial degree of heterogeneity, a random effects model was also applied (RR 1.54 (95 % CI 0.81-2.92)) (Figure 2b). The quality of evidence was low (Table 3). The risk difference was 0.02 and NNH 50.

Primary outcome: Depression

The risk of depression was assessed in four RCTs (20–23) through patient reported questionnaires. In two studies a non-significant decrease in risk of feeling depressive symptoms was found (20,21). In the other two studies, an increase in risk of feeling depressed was found (22,23), one was statistically significant(23). Risk of bias were unclear in two RCT's(21,23) and low in two others(20,22), due to no blinding or uncertainty about blinding of personal, participants or outcome assessors. All four studies supplied data for meta-analysis. The summary RR involving 5,564 women with 196 events was 1.48 (95 % CI 1.09-2.02) (Figure 3a) with a high degree of statistical heterogeneity (I^2= 78 %). The results became statistically insignificant when applying a random effects model (RR of 1.58 (95 % CI 0.70-3.59)) (Figure 3b). We assessed the quality of evidence as very low (Table 3). The risk difference was 0.01 and NNH 100.

Primary outcome: Ovarian cysts

The risk of developing ovarian cysts after insertion of a LNG-IUS was assessed in two RCTs (20,24). An increased risk of ovarian cysts was found in both studies, one of these was significant(20). Risk of bias was unclear in one RTC(24), due to unclear blinding of participants, personal and outcome assessors, while it was low in the other study(20). Both studies supplied data for meta-analysis. The summary RR involving 2,341 women and 64 events was 2.59 (95 % CI 1.51-4.44) (Figure 4) with no degree of statistical heterogeneity (I^2= 0 %). The quality of evidence was moderate (Table 3). The risk difference was 0.02 and NNH was 50.

Amenorrhea

The risk of developing amenorrhea within a year after insertion of a LNG-IUS was assessed in seven RCTs[23–28,29]. Amenorrhea was defined as lack of bleeding for more than 90 days. Information was primarily obtained through bleeding diaries. All of the RCTs reported an increased risk of amenorrhea after insertion, six of these were significant[23–26,28,29]. The risk of bias was unclear in five of the RCTs(22,24–27) due to an absence or uncertainty about blinding of personal, participants or outcome assessors, and low in two studies(20,22). All studies supplied data for meta-analysis. The summary RR involving 7,903 women with 1,088 events was 6.22 (95 % CI 5.21-7.43) (Figure 5) with no degree of statistical heterogeneity (I^2=5%). The GRADE estimate for quality of evidence was moderate (Table 3). An asymmetric Funnel plot was generated based on the RR's, indicating possible publication bias (Figure 6). The quality of evidence was upgraded because of the very large effect. An upgrade in quality because of a large effect is usually done in observational studies(27) but is applied here due to the summary RR of 6.22. The risk difference was 0.19 and NNH 5.2.

Acne

The risk of developing acne was assessed in four RCTs(20,21,23,25), and data was obtained through questionnaires and interviews. In all studies, an increased risk of developing acne was found. In two studies the increased risk was significant(23,25). The risk of bias was unclear in two of the studies(21,23), due to no blinding or uncertainty about blinding of personal, participants or outcome assessors, and low in the other two studies(20,22). All studies supplied data for meta-analysis. The summary RR involving 5,567 women and 199 events was 2.65 (95 % CI 1.86-3.77) (Figure 7a) with a substantial degree of heterogeneity (I^2= 66 %). The result remained significant when applying a random effects model (RR 2.49 (95 % CI 1.28-4.81)) (Figure 7b). The quality of evidence was very low (Table 3). The risk difference was 0.03 and NNH 33.3.

Headaches

The correlation between headaches and LNG-IUS was assessed in five RCTs(20–23,28). One study found an insignificant decrease in headaches(28), the other four studies found an increased risk(20–23). In three of these studies the increased risk was significant(20,22,23), while the study showing insignificant results was small with only 80 participants and seven events(21). The risk of bias was unclear in three of the studies(21,23,28), due to no blinding or uncertainty about blinding of personal, participants or outcome assessors, and low in two studies(20,22). All studies supplied data for meta-analysis. The summary RR involving 5,883 women and 680 events was 1.58 (95 % CI 1.37-1.83) (Figure 8a), with a high degree of

heterogeneity (I^2=83 %). The result became insignificant when applying a random effects model (RR 1.60 (95 % CI 0.96-2.67)) (Figure 8b). The quality of evidence was very low (Table 3). The risk difference was 0.05 and NNH 20.

Breast discomfort

The risk of increased breast discomfort after insertion of LNG-IUS was assessed in three RCTs(20,23,28). Data was obtained through questionnaires and reported as breast tenderness(23,28) and mastalgia(20). One large-scale study found a significant increase in risk of breast discomfort(23), the other two studies found a near significant increase(20,28). The risk of bias was unclear in two of the studies(23,28) due to no blinding or uncertainty about blinding of personal, participants or outcome assessors, and low in one study(20). All studies supplied data usable for meta-analysis. The summary RR involving 5,310 women and 279 events was 1.63 (95 % CI 1.28-2.09) (Figure 9a), with a high degree of heterogeneity (I^2 = 85%). This result became statistically insignificant when applying a random effects model (RR 2.32 (95 % CI 0.92-5.81)) (Figure 9b). The quality of evidence was very low (Table 3). The risk difference was 0.03 and NNH 33.3.

Weight gain

The risk of weight gain due to treatment with an LNG-IUS was assessed in four RCTs(20,22–24) and one study of uncertain type(20). In four of the studies weight gain was reported as a continuous outcome(20,23–25) and in the remaining study it was reported as a binary outcome(20). One study found no difference in weight change at all(23). Three studies found LNG-IUS to induce weight gain(20,21,23) while one study found LNG-IUS to induce weight loss(24). None of these were significant. Risk of bias was unclear in all studies(20,21,23–25) due to no blinding or uncertainty about blinding of personal, participants or outcome assessors. Data from the four studies that reported weight gain as a continuous outcome was included in the meta-analysis. In the study that reported weight gain as a binary outcome, the RR was 0.97 (95 % CI 0.57-1.63) (Figure 10).

In the meta-analysis the mean difference summarizing 3,178 women was 0.001 (95 % CI -0.74-0.76) (Figure 11) with no heterogeneity (I^2=0%). The quality of evidence was low (Table 3).

Research Question 2

Only one RCT was found eligible for Research Question two (30). This RCT had 738 participants and compared the number of pregnancies, bleeding pattern and adverse effects between a high-dose LNG-IUS and two low-dose LNG-IUS. The risk of bias in the study was low.

The study found three ectopic pregnancies in women treated with low-dose LNG-IUS compared to none in women treated with high-dose LNG-IUD (RR of 3,68 (95 % CI 0.19-70.98)). In addition, the study found an increased risk of mood swings when treated with a low dose LNG-IUS (RR of 1.45 (95 % CI 0.94-2.23)) and a decreased risk of developing ovarian cysts (RR of 0.33 (95 % CI 0.22-0.49)).
The study found a decreased risk of headaches (RR of 0.56 (95 % CI 0.40-0.78)) The risk of breast discomfort (RR of 1.16 (95 % CI 0.85-1.59)), acne (RR of 0.78 (95 % CI 0.60-1.01)) and weight gain was unchanged (RR of 1.37 (0.85-2.22)).

Discussion

Main findings

To the best of our knowledge this is the first systematic review with meta-analysis examining short-term side-effects from using an LNG-IUS and comparing these side-effects and number of ectopic pregnancies in different dosages of LNG-IUS's.
Our review and meta-analysis yielded several findings. For Research Question 1 our primary outcomes were changes in mood and frequency of ovarian cysts. In the studies included for Research Question 1 mood changes were not reported. However, multiple studies reported an increased nervousness and an increase of depressive symptoms and we accepted this as surrogates for our outcome. It should be noted, that in the included articles, no definitions of nervousness or depressive symptoms were given. We found a statistically significant increase in nervousness and depressive symptoms after insertion of an LNG-IUS, but the meta-analyses revealed a high degree of heterogeneity. When a random-effects model was used an increase was still found but it was not statistically significant, and the quality of evidence were very low for both outcomes. For Research Question 1, we found a statistically significant increase in risk of developing ovarian cysts. Only two studies and very few events were included, but with a low heterogeneity the quality of evidence was assessed as moderate. For Research Question two our primary outcomes were changes in mood, frequency of ovarian cysts and ectopic pregnancies. In the one study that was included for Research Question 2, a non-statistically significant increase in mood swings was found among women treated with a low-dose LNG-IUS. A statistically significant decreased risk of developing ovarian cysts was also found in the study. However, the results are unclear due to very few reported events and lack of more studies. Likewise, the results on ectopic pregnancies are unclear due to small number of events.
A secondary outcome result that should be mentioned as well is a substantial statistically significant increase in the risk of developing amenorrhea within a year after insertion of an LNG-IUS. The quality of evidence was moderate and has been upgraded due to a very large effect size. A Funnel Plot was created for this outcome (Figure 6) and it was asymmetric indicating possible publication bias but might also be due

to an apparent increase in risk of developing amenorrhea.

It is important to note that even though we found an increased risk for multiple outcomes only a few percentages of the participants experienced reported on the outcomes and the absolute risk for the outcomes are low.

Strengths and limitations

This is a comprehensive assessment of the evidence, mainly from RCTs and without geographical restrictions. The use of the GRADE approach to evaluate the quality of the results and the fact that there was no clinical heterogeneity is also recognized as a strength.

We recognize several limitations to this systematic review. For some outcomes, very few events were reported. We calculated NNH for all continues outcomes, due to the benefits from its intuitive comprehension, even though the use of NNH is discouraged by some statisticians(16).

A noteworthy limitation is that only one study was included for Research Question two, not enabling us to perform a meta-analysis on this matter. All outcomes, except for ovarian cysts, were in all studies assessed from questionnaires. Therefore, the results rely on the participants estimate of e.g. an increase in nervousness or acne which might lead to performance bias in studies that were not blinded thus causing a false high RR. Furthermore, the studies had no definitions of acne, depression or nervousness which may have led to misclassification by the participants when they reported their subjective findings.

Another limitation is that in many of the studies, the event rates for side-effects are recorded at the end of the study and only for active participants. In most studies, reasons for terminations are noted as 'hormonal' and are not included in the total event rate. Furthermore, participants that discontinued with an LNG-IUS for other reasons than 'hormonal' might also have experienced the side-effects that were investigated in the study, possibly underestimating the RR.

Interpretation

In line with a newly published systematic review that included studies from multiple countries on high-dose LNG-IUS (31), we found a highly increased risk of developing amenorrhea after insertion of an LNG-IUS.

To our knowledge, no systematic reviews investigating our other desired outcomes have been published and our search has not revealed any previous reviews on side-effects of different dosages of LNG-IUS's.

A prospective cohort study found an increased RR of first use of an antidepressant among women with an LNG-IUS compared to non-users of hormonal contraception. This correlates with our findings of an

increased risk of feeling more depressed after insertion. Clinicians should be cautious when prescribing a form of hormonal contraception to women already diagnosed with depression or known to have a tendency towards depressive symptoms.

A newly published study from Sweden found a higher incidence of ectopic pregnancies among women with low-dose LNG-IUS compared to women with high-dose LNG-IUS(32). This study did not meet our inclusion criteria, and the one study included for Research Question 2 did not report a clear result on ectopic pregnancies.

Conclusion

We found an increased risk of changes in mood, ovarian cysts, acne, breast discomfort, amenorrhea and headaches. However, except from the results on amenorrhea and ovarian cysts, these results should be interpreted with caution given the low quality of evidence. We found no increased risk of weight gain. Our review only included one study comparing different dosages of LNG-IUS. The study found a decreased risk of developing ovarian cysts when treated with a low-dose LNG-IUS but the risk of mood swings and ectopic pregnancies were unclear.

Our review might assist clinicians in counselling women seeking contraception but to achieve higher quality of evidence further data are needed. This should preferably be from RCTs or large-scale, prospective cohort studies in which participants and outcome assessors should be blinded and all outcomes should be assessed by clinicians. Furthermore, studies with short-term side-effects as primary outcome are needed as well as a comparison of the rate of ectopic pregnancies related to dosage of the LNG-IUS.

Disclosure of interest

The authors have declared that there is no conflict of interests.

Contribution to authorship

JBS and EHI conceived the idea of the meta-analysis and designed the inclusion and exclusion criteria. JBS designed the literature search. EHI and HTW designed the data collection forms and screened all abstracts, selected eligible papers and extracted data. EHI and JBS performed the analysis. EHI wrote the first draft of the paper, JBS and HTW reviewed the manuscript critically.

Details of ethics approval

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Tables:

Table 1. Key features of of available levonorgestrel-releasing intrauterine systems(5)

Device (brand name)	Total levonorgestrel content	Daily LNG rate	Approved duration of use
LNG IUS 20 (Mirena)	52 mg	20 µg/day	5 years
LNG 20 (Liletta)	52 mg	18.6 µg/day	3 years
LNG IUS 8 (Jaydess/Skyla)	13.5 mg	8 µg/day	3 years
LNG IUS 9 Kyleena	19.5 mg	9 µg/day	5 years

Table 2. Characteristics of studies and outcomes

Research Question 1

erence, year, country	Study design, study period, participants (n)	Exposure / control	Outcome prevalence % (n/N)				
			Depression	Nervousness	Ovarian cysts	Amenorrhea	Breast discomfort
kkila, 1982, Finland	Single blinded RCT, 1 year, n: 80	LNG-30 IUD / Cu-IUD	7.5 (3/40)	12.5 (5/40)	-	22,5 (9/40)	-
son, 1982, Finland/Brazil	Double blinded RCT, 1 year, n: 483	LNG-43/56 IUD/ Cu-IUD	12.7 (41.5/327)	23.2 (76/327)	-	11 (36/327)	-
kkainen, 1987, mark/Finland/Hungary/Norwa	Open RCT, 1 year, n: 2758	Mirena/Cu-IUD	-	-	-	1.6 (22/1362)	-
lersson, 1994, and/Denmark/Hungary/Norwa	Open RCT, 5 years, n: 2758	Mirena / Cu-IUD	2.5 (46/1821)	-	-	16.8 (306/1821)	3.1 (56/1821)
n , 1994, Developing countries	RCT, 7 years, n: 2246	LNG-46/60-IUD/ Cu-IUD	3.6 (41/1121)	4.2 (48/1121)	3.6 (41/1121)	49.1 (550/1121)	8.6 (96/1121)
Ava, 2012, Brazil	Uncertain study design, 1 year, n: 86	Mirena/Cu-IUD	-	-	-	-	-
desto, 2014, Brazil	Open RCT, 1 year, n: 199	Mirena /Cu-IUD	-	-	-	35 (35/99)	

ehan, 2015, Turkey	RCT, 6 months, n: 100	Mirena/ Cu-IUD	-	-	11.1 (5/45)	8.8 (4/45)	-
k, 2019, Egypt	Open RCT, 6 months, n: 306	Mirena / Cu-IUD	-	-	-	-	18.4 (28/152)

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417 Research Question 2:

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Reference, year, country	**Study design, study period, participants (n)**	**Exposure / control**	**Outcome prevalence % (n/N)**					
			Ectopic pregnancies	Depression	Nervousness	Ovarian cysts	Amenorrhea	Breast discomfort
Gemzell-Danielsson , 2012, Finland/Sweden , Norway, Hungary, United Kingdom	Open RCT, 3 years, n: 738	LNG-12/16-IUS/ Mirena	0.6 (3/484)	16.3 (79/484)	-	7.2 (35/484)	-	21.07 (102/484)

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420 Table 3. Summary of findings table.
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Question 1, LNG-IUS compared to non-hormonal contraception on short-term systemic side-effects

Patient or population: Women seeking contraception
Intervention: LNG-IUS
Comparison: Non-hormonal contraception (copper intrauterine system)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non	Risk with PICO1 Hormone IUS				
Amenorrhea	41 per 1.000	**254 per 1.000** (213 to 303)	**RR 6.22** (5.21 to 7.43)	7903 (7 RCTs)	⨁⨁⨁◯ MODERATE [a,b]	
Weight gain	The mean weight gain was **0**	MD **0.01 higher** (0.74 lower to 0.76 higher)	-	3254 (4 RCTs)	⨁⨁◯◯ LOW [c]	
Ovarian cysts	15 per 1.000	**40 per 1.000** (23 to 68)	**RR 2.59** (1.51 to 4.44)	2341 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	
Acne	18 per 1.000	**44 per 1.000** (23 to 85)	**RR 2.49** (1.28 to 4.81)	5567 (4 RCTs)	⨁◯◯◯ VERY LOW [e]	
Headache	101 per 1.000	**162 per 1.000** (97 to 270)	**RR 1.60** (0.96 to 2.67)	5883 (5 RCTs)	⨁◯◯◯ VERY LOW [f]	
Nervousness	51 per 1.000	**71 per 1.000** (53 to 95)	**RR 1.40** (1.04 to 1.87)	2809 (3 RCTs)	⨁⨁◯◯ LOW [g]	
Depression	28 per 1.000	**45 per 1.000** (20 to 102)	**RR 1.58** (0.70 to 3.59)	5567 (4 RCTs)	⨁◯◯◯ VERY LOW [h]	
Breast discomfort	45 per 1.000	**104 per 1.000** (41 to 260)	**RR 2.32** (0.92 to 5.81)	5310 (3 RCTs)	⨁◯◯◯ VERY LOW [i]	

Explanations
a. Downgraded to due risk of bias (all studies have low risk of bias or unclear risk of bias, but there are major concerns of blinding in three studies and incomplete data not addressed in one study) and due to the asymmetric Funnel Plot (Figure 6) that might indicate publication bias.
b. Upgraded due to the large effect.
c. Downgraded due to risk of bias and wide confidence intervals.
d. Downgraded due to uncertainty about blinding in one of the studies.
e. Downgraded due to risk of bias (iIn this case uncertainty about blinding or no blinding applied. In Lukkainen 1987, participants were informed of potential side-effects) and high heterogeneity (I 2 =66 %).
f. Downgraded due to risk of bias and high heterogeneity (I 2 =85 %)
g. Downgraded due to risk of bias, high heterogeneity (I2= 68%) and wide CI.
h. Downgraded due to high heterogeneity (I2= 78 %), few events, and wide CI.
i. Downgraded due to risk of bias, high heterogeneity, wide CI and few events.