Supplementary Appendix. Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables for recommendations reviewed, *U.S. Selected Practice Recommendations for Contraceptive Use, 2024*. (Curtis KM, Nguyen AT, Tepper N, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2024. MMWR Recomm Rep 2024;73[No. RR-3]:1–77. https://www.cdc.gov/mmwr/volumes/73/rr/rr7303a1.htm)

Table of Contents

1. Testosterone and risk for pregnancy

Systematic review question: Among transgender, gender diverse, and nonbinary persons with a uterus, who are using testosterone, what is the magnitude of risk of pregnancy? This table is based on Halper E, Meurice ME, Curtis KM, Nguyen A, Obedin-Maliver J, Suresh T, Whiteman MK. Pregnancy risk and contraceptive safety among transgender, gender diverse, and nonbinary persons individuals with a uterus, who are using testosterone therapy: A systematic review. Contraception 2024: in preparation.

Methods: All effects presented below are from individual estimates; no meta-analysis was conducted.

Outcome	Number of Studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Testosterone users										
Ovulation (PdG > 5 µg/mL for 3 consecutive days)	1[1]	Non-comparative cohort	Very serious[a]	Not serious	Very serious[b]	Serious[c]	22	N/A	1/22 (5%) ovulated; 1/6 (17%) of new users and 0/16 (0%) of continuing users	Very low
Ovulation (PdG > 3 µg/mL for 2 consecutive days)	1[1]	Non-comparative cohort	Very serious[a]	Not serious	Very serious[b]	Serious[c]	22	N/A	8/22 (36%) ovulated; 6/6 (100%) of new users and 2/16 (13%) of continuing users	Very low

PdG, pregnanediol-3-glucuronide; N/A, not applicable

Footnotes

[a]Risk of bias is considered very serious due to the low response and follow-up rates.

[b]Imprecision is considered very serious due to the small sample size.

[c]Indirectness is considered serious due to the use of ovulation as a proxy measure for pregnancy risk.

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2. Provision of medications for intrauterine device (IUD) placement

2.1 Evidence summary for additional interventions for which evidence suggested no positive effect or evidence was too limited to make a recommendation

Evidence on several other interventions was identified, including lidocaine as an intracervical block (1 trial), intrauterine instillation (4 trials), analgesics (17 trials on 7 different interventions), smooth muscle relaxants (6 trials on 5 different interventions), and dinoprostone (5 trials). For these interventions, the evidence either suggested no positive effect on the outcomes assessed or the evidence was too limited to make a recommendation. A detailed summary of the evidence is provided below for each intervention.

Intervention category	Intervention details	Evidence summary	Certainty of evidence
Lidocaine as an intracervical block	Evidence for lidocaine as an intracervical block includes one trial of 2% lidocaine (3.6 mL) administered as 4-point injections (timing of administration not reported) (Section 2.3.1).	• Evidence suggests that lidocaine as an intracervical block might reduce patient pain at tenaculum placement and during IUD placement and might reduce vasovagal reaction compared with no treatment and compared with placebo/sham block. • Evidence suggests that lidocaine as an intracervical block does not reduce adverse events or need for adjunctive placement measures (i.e., cervical dilation), nor improve provider ease of placement or placement success. • No evidence on side effects or patient satisfaction with the procedure was found.	Moderate for patient pain, provider ease of placement, need for adjunctive placement measures, and placement success; low for adverse events.
Intrauterine instillation	Evidence for intrauterine instillation of a local anesthetic includes 4 randomized controlled trials (Section 2.3.3). One trial examined 2% lidocaine intrauterine instillation (1.2 mL) infused into the lower one-third, the middle, and the top of the endometrial cavity three minutes before IUD placement. Another trial examined 4% lidocaine gel intrauterine instillation (5.5 mL) infused into the uterine cavity five minutes before IUD	• Evidence on intrauterine instillation of a local anesthetic generally suggested no positive effect on patient pain. • One meta-analysis of three interventions (two trials), another meta-analysis of two interventions (one trial), and one randomized controlled trial found no differences in patient pain at either tenaculum placement, during IUD placement, or after IUD placement before clinic discharge. One trial did find intrauterine instillation of 1%	High for placement success; moderate for patient pain, provider ease of placement, need for adjunctive placement measures, and patient satisfaction with the procedure.

Intervention category	Intervention details	Evidence summary	Certainty of evidence
	placement; 1 mL was also placed on the surface of the cervix and 2 mL was placed in the cervical canal. The third trial examined 1% mepivacaine intrauterine instillation (10 mL) infused (exact location not specified) five minutes before IUD placement. The fourth trial examined two interventions: 2% lidocaine intrauterine instillation (5 mL) infused through the endocervix plus oral naproxen, and 2% lidocaine intrauterine instillation (5 mL) infused through the endocervix plus placebo pills; for both interventions, administration was five minutes before IUD placement for the instillation and one hour before IUD placement for the oral pills.	mepivacaine (10 mL) five minutes before IUD placement was associated with reduced pain after IUD placement before clinic discharge. This trial also found that 1% mepivacaine (10 mL) instilled five minutes before IUD placement was associated with reduced need for analgesia at the clinic. • Evidence suggests that intrauterine instillation of a local anesthetic does not improve provider ease of placement, placement success, or patient satisfaction with the procedure. • No evidence on adverse events or side effects was found.	
Analgesics (overall)	Evidence for analgesics includes 17 randomized controlled trials (Section 2.4).		
NSAIDs	Twelve trials examined nonsteroidal anti-inflammatory drugs (NSAIDs), including four that examined oral ibuprofen (200-800 mg), two that examined ketorolac (1 oral, 20 mg and 1 intramuscular injection, 30 mg), three that examined oral naproxen (375-550 mg), one that examined oral ketoprofen (150 mg), one that examined oral etoricoxib (120 mg), and one that examined indomethacin as a rectal	• Evidence on NSAIDs generally suggested no positive effect on patient pain or patient satisfaction with the procedure. • One meta-analysis of two trials, another meta-analysis of two trials, and one meta-analysis of five trials, plus seven randomized controlled trials found no differences in patient pain at either tenaculum placement, during IUD placement, or after IUD placement before clinic discharge between patients receiving NSAIDs compared with	High for placement success; moderate for patient pain, need for adjunctive placement measures, side effects, and patient satisfaction with the procedure; low for provider ease

Intervention category	Intervention details	Evidence summary	Certainty of evidence
	suppository (50 mg). The timing of NSAID administration was one hour or less before IUD placement in most trials; two trials examined NSAIDs administered one to four hours or one to one and a half hours before IUD placement.	placebo. One trial did find patients receiving indomethacin (50 mg) as a rectal suppository 30 minutes before IUD placement had reduced pain at tenaculum placement and during IUD placement compared with those receiving placebo. • One meta-analysis of three trials and two randomized controlled trials found no differences in patient satisfaction with IUD placement (*3*). One trial did find patients receiving oral naproxen (550 mg) one hour before IUD placement were less likely to report IUD placement as unpleasant or very unpleasant compared with those receiving placebo. • Evidence suggests that NSAIDs do not reduce adverse events or need for cervical dilation, increase side effects (specifically nausea, vomiting, dizziness, or drowsiness), nor improve provider ease of placement or placement success. One meta-analysis of four trials found reduced need for additional analgesia.	of placement and adverse events.
NSAID plus lidocaine	Two trials examined an NSAID plus lidocaine; one examined 100 mg oral diclofenac one hour before IUD placement plus 2% lidocaine topical gel (cervical) applied three minutes before IUD placement, and the other examined 375 mg oral naproxen one hour before IUD placement plus 2% lidocaine intrauterine instillation (5 mL) infused at least three minutes before IUD placement.	• Evidence from two trials suggests that an NSAID plus lidocaine does not reduce patient pain or adverse events, nor improve provider ease of placement, placement success, or patient satisfaction with the procedure. • No evidence on adjunctive placement measures or side effects was found.	Moderate for patient pain and provider ease of placement; low for placement success, adverse events, and patient satisfaction with the procedure.

Intervention category	Intervention details	Evidence summary	Certainty of evidence
NSAID plus smooth muscle relaxant	One trial examined an NSAID (mefenamic acid, 250 mg) plus a smooth muscle relaxant (drotaverine, 80 mg), taken orally 30 minutes before IUD placement.	• Evidence from one trial suggests that mefenamic acid (250 mg) plus drotaverine (80 mg) 30 minutes before IUD placement might reduce patient pain during IUD placement, but does not improve placement success. • No evidence on provider ease of placement, need for adjunctive placement measures, side effects, adverse events, or patient satisfaction with the procedure was found.	Low for patient pain and placement success.
Tramadol	Two trials examined oral tramadol (50 mg) administered one hour before IUD placement.	• Evidence from two trials suggests that tramadol (50 mg) one hour before IUD placement might ease placement and improve patient satisfaction. ○ One trial found that tramadol was associated with improvement in provider ease of placement, and the other trial found that tramadol was associated with reduced patient report of IUD placement being unpleasant or very unpleasant compared with patients receiving placebo. • Evidence from the two trials suggests that tramadol does not reduce patient pain, nor improve placement success, and evidence from one trial suggests that tramadol does not reduce adverse events. • One trial examined side effects (specifically nausea, vomiting, and dizziness) and observed zero events in either study group. • No evidence on adjunctive placement measures was found.	Low for provider ease of placement, placement success, side effects, adverse events, and patient satisfaction with the procedure; very low for patient pain.

Intervention category	Intervention details	Evidence summary	Certainty of evidence
Acetaminophen	One trial examined oral acetaminophen (500 mg) administered 20 minutes before IUD placement.	• Evidence from one trial that examined acetaminophen (500 mg) 20 minutes before IUD placement compared with no treatment suggests acetaminophen does not reduce patient pain nor improve placement success. • No evidence on provider ease of placement, need for adjunctive placement measures, side effects, adverse events, or patient satisfaction with the procedure was found.	Low for patient pain and placement success.
Nitrous oxide	One trial examined 50% nitrous oxide (timing of administration not reported).	• Evidence from one trial found that 50% nitrous oxide for IUD placement reduced nausea and increased patient satisfaction with pain management during IUD placement among patients receiving nitrous oxide versus controls. • Evidence from this trial found that 50% nitrous oxide did not reduce patient pain, nor improve provider ease of placement or placement success. • No evidence on adjunctive placement measures or adverse events was found.	Moderate for patient pain, provider ease of placement, placement success, side effects, and patient satisfaction with the procedure.
Smooth muscle relaxants (overall)	Evidence for smooth muscle relaxants includes six randomized controlled trials (Section 2.5).		
Topical	Three trials examined topical smooth muscle relaxants, including nitroprusside gel (1 mL), applied intracervically immediately before IUD placement; nitroglycerin ointment (1 mL), applied at the posterior fornix 30-45 minutes before IUD placement; and nitroglycerin cream (glyceryl trinitrate [GTN], 2 mL),	• Evidence on topical smooth muscle relaxants generally suggested no positive effect on patient pain, provider ease of placement, or patient satisfaction with the procedure. • Two trials that examined nitroprusside gel or nitroglycerin ointment found no differences in patient pain during IUD placement or after IUD placement before clinic discharge, provider ease of	Moderate for patient pain, provider ease of placement, patient satisfaction with the procedure; high for need for adjunctive placement measures, placement success,

Intervention category	Intervention details	Evidence summary	Certainty of evidence
	applied to the anterior cervical lip and inserted into the cervix three minutes before IUD placement.	placement, or patient satisfaction with the procedure. One trial found that nitroglycerin cream reduced patient pain at tenaculum placement, during IUD placement, and after IUD placement before clinic discharge, improved provider ease of placement, and increased patient satisfaction with the procedure. • Evidence suggests that topical smooth muscle relaxants do not reduce adverse events, side effects, or need for adjunctive placement measures, nor improve placement success.	side effects, and adverse events.
NSAID plus smooth muscle relaxant	One trial examined an NSAID (mefenamic acid, 250 mg) plus a smooth muscle relaxant (drotaverine, 80 mg), taken orally 30 minutes before IUD placement.	• Evidence from one trial suggests that mefenamic acid (250 mg) plus drotaverine (80 mg) might reduce patient pain during IUD placement, but does not improve placement success. • No evidence on provider ease of placement, need for adjunctive placement measures, patient side effects, adverse events, or patient satisfaction with the procedure was found.	Moderate for patient pain and placement success.
Isonicotinic acid hydrazide	Two trials examined isonicotinic acid hydrazide (900 mg), inserted vaginally 12 hours before IUD placement in one trial and inserted vaginally six hours before IUD placement in the other.	• Evidence from two trials suggests that isonicotinic acid hydrazide (900 mg) inserted vaginally six or 12 hours before IUD placement reduces patient pain at either tenaculum placement, during IUD placement, or after IUD placement before clinic discharge, and improves provider ease of placement and patient satisfaction with the procedure. • One trial found that isonicotinic acid hydrazide (900 mg) inserted vaginally 12 hours before IUD placement reduced the need for cervical dilation.	High for patient pain, provider ease of placement, patient satisfaction with the procedure, and side effects; moderate for placement success; low for need for adjunctive placement measures (cervical dilation).

Intervention category	Intervention details	Evidence summary	Certainty of evidence
		• Evidence suggests that isonicotinic acid hydrazide does not reduce side effects, nor improve placement success. • No evidence on adverse events was found.	
Dinoprostone	Evidence for dinoprostone includes 5 randomized controlled trials assessing 3 mg vaginal dinoprostone, administered 2-12 hours before IUD placement, compared with placebo (Section 2.6) .	• Evidence suggests that dinoprostone does not reduce patient pain or adverse events, nor improve provider ease of placement or patient satisfaction with the procedure. • Evidence from one meta-analysis of four trials suggests that dinoprostone reduces the need for additional analgesia after the procedure before clinic discharge. • Evidence suggests that dinoprostone increases fever but is not associated with other side effects (nausea, vomiting, diarrhea, shivering, abdominal cramps, or post-procedural bleeding). • No evidence on placement success was found.	High for patient pain, provider ease of placement, need for additional analgesia before clinic discharge, and patient satisfaction; low for side effects and very low for adverse events.

2.2 Provision of medications for intrauterine device (IUD) placement: Misoprostol

Systematic review question: Among patients receiving an interval IUD (i.e., placement outside the postabortion or postpartum period), does the use of misoprostol affect patient or provider outcomes compared with placebo or no treatment? This table is based on Zapata LB, Nguyen AT, Snyder E, Napp K, Ti A, Whiteman MK, Curtis KM. Misoprostol for intrauterine device placement. Cochrane Database of Systematic Reviews 2024: In preparation.

Methods: All effects presented below are from pooled meta-analysis, except when the number of studies was one.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Misoprostol vs. placebo/control										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	3[1-3]	RCT	Not serious	Not serious	Not serious	Not serious	130	131	Mean difference (95% CI): -0.73 (-1.19, -0.28) (p=0.002)	High
Pain during IUD placement (10 cm VAS [mean])	7[1-7]	RCT	Not serious	Serious[a]	Serious[b]	Not serious	386	380	Mean difference (95% CI): -0.43 (-1.30, 0.44) (p=0.33)	Low
Moderate or severe pain during IUD placement (%)	3[8-10]	RCT	Serious[c]	Serious[a]	Serious[b]	Not serious	329	339	Risk ratio (95% CI): 0.82 (0.58, 1.16) (p=0.26)	Very low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	5[1-3, 7, 11]	RCT	Not serious	Serious[a]	Not serious	Not serious	226	222	Mean difference (95% CI): 0.08 (-0.59, 0.74) (p=0.82)	Moderate
Pain during IUD placement (10 cm VAS [median])	1[12]	RCT	Serious[d]	Not serious	Serious[e,f]	Not serious	39	40	Median (range): 7.0 (2.5-10) for misoprostol group vs. 6.5 (0-10) for control group (p=0.20); median difference: 0.5	Low
Pain during IUD placement (10 cm VAS [median])	1[13]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	37	36	Median (range): 4.6 (1.1-9.2) for misoprostol group vs. 3.4 (0-9.0) for control group (p=0.044); median difference: 1.2	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[13]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	37	36	Median (range): 3.6 (0.1-10.0) for misoprostol group vs. 2.1 (0-8.6) for control group (p=0.024); median difference: 1.5*	Moderate
Provider Ease of Placement										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Easy placement (%)	3[8, 10, 12]	RCT	Not serious	Serious[a]	Serious[b]	Not serious	168	179	Risk ratio (95% CI): 1.30 (0.85, 1.98) (p=0.24)	Moderate
Provider ease of placement (10 cm VAS [mean])	8[1-7, 11]	RCT	Not serious	Serious[a]	Serious[b]	Not serious	428	420	Mean difference (95% CI): -0.85 (-1.65, -0.05) (p=0.04)	Low
Provider ease of placement (10 cm VAS [median])	1[13]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	37	36	Median (range): 2.1 (0-10) for misoprostol group vs. 2.1 (0-6.8) for control group (p=0.75); median difference: 0.0	Moderate
Need for Adjunctive Placement Measures										
Ultrasound guidance (%)	3[6, 7, 13]	RCT	Not serious	Not serious	Serious[b,f]	Not serious	121	118	Risk ratio (95% CI): 0.71 (0.09, 5.86) (p=0.75)	Moderate
Local anesthesia (%)	5[2, 6-8, 13]	RCT	Not serious	Not serious	Serious[b,f]	Not serious	181	182	Risk ratio (95% CI): 1.31 (0.85, 2.04) (p=0.22)	Moderate
Analgesia (%)	1[8]	RCT	Not serious	Not serious	Serious[f]	Not serious	43	46	Peto odds ratio (95% CI): not estimable due to 0 events observed	Moderate
Cervical dilation (for patients with recent failed placement attempt) (%)	1[14]	RCT	Not serious	Not serious	Serious[b,f]	Not serious	48	42	Risk ratio (95% CI): 0.88 (0.56, 1.36) (p=0.55)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Cervical dilation (for patients without recent failed placement attempt) (%)	6[2, 5-8, 13]	RCT	Not serious	Not serious	Serious[b]	Not serious	283	279	Risk ratio (95% CI): 0.84 (0.38, 1.85) (p=0.66)	Moderate
Placement Success										
Placement success (for patients without recent prior failed placement attempt) (%)	12[1-7, 9-13]	RCT	Not serious	Serious[a]	Not serious	Not serious	790	789	Risk ratio (95% CI): 1.01 (0.98, 1.04) (p=0.42)	Moderate
Placement success (for patients with recent prior failed placement attempt) (%)	1[14]	RCT	Not serious	Not serious	Serious[b,f]	Not serious	48	42	Risk ratio (95% CI): 1.41 (1.09, 1.83) (p=0.009)*	Moderate
Side Effects										
Nausea (%)	8[1, 2, 5, 6, 8, 10-12]	RCT	Not serious	Not serious	Serious[b]	Not serious	399	404	Risk ratio (95% CI): 1.42 (0.80, 2.55) (p=0.24)	Moderate
Vomiting (%)	6[1, 2, 6, 10-12]	RCT	Not serious	Not serious	Serious[b]	Not serious	257	266	Risk ratio (95% CI): 2.14 (0.77, 5.91) (p=0.14)	Moderate
Diarrhea (%)	9[1, 2, 4-6, 8, 10-12]	RCT	Not serious	Not serious	Serious[b]	Not serious	469	471	Risk ratio (95% CI): 1.76 (1.01, 3.06) (p=0.04)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Pre-placement abdominal pain/cramping (%)	7[1, 2, 4-6, 8, 10]	RCT	Not serious	Serious[a]	Serious[b]	Not serious	388	393	Risk ratio (95% CI): 2.14 (1.42, 3.23) (p=0.0003)*	Low
Adverse Events										
Uterine perforation (%)	7[1, 3-6, 8, 10]	RCT	Not serious	Not serious	Very serious[f]	Not serious	444	450	0/444 vs. 0/450; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vasovagal reaction (%)	6[1-5, 10]	RCT	Not serious	Not serious	Serious[b,f]	Not serious	388	392	9/388 vs. 10/392; Peto odds ratio (95% CI): 0.94 (0.37, 2.37) (p=0.89)†	Moderate
Patient Satisfaction with Procedure (assessed before clinic discharge)										
Patient satisfaction with procedure (10 cm VAS [mean])	2[1, 4]	RCT	Not serious	Not serious	Serious[b]	Not serious	113	113	Mean difference (95% CI): 2.00 (-0.05, 4.06) (p=0.06)	Moderate

CI, confidence interval; IUD, intrauterine device; RCT, randomized clinical trial; VAS, visual analog scale

Footnotes

*Effect was statistically significant and clinically relevant.

†Three studies had non-estimable peto ORs; peto OR represents data from three studies

[a]Inconsistency is considered serious due to varying results among studies.

[b]Imprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

[c]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes in one study.

[d]Risk of bias is considered serious due to the outcome being self-reported by participants who were not blinded to group allocation in one study.

[e]Imprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

[f]Imprecision is considered serious due to the small sample size.

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2.3 Provision of medications for intrauterine device (IUD) placement: Local anesthetics

Systematic review question: Among patients receiving an interval IUD (i.e., placement outside the postabortion or postpartum period), does the use of local anesthetics affect patient or provider outcomes compared with placebo or no treatment? This table is based on Zapata LB, Nguyen AT, Snyder E, Whiteman MK, Napp K, Ti A, Curtis KM. Local anesthetics for intrauterine device placement. Cochrane Database of Systematic Reviews 2024: In preparation.

Methods: All effects presented below are from pooled meta-analysis, except when the number of studies was one.

2.3.1 Lidocaine as paracervical or intracervical block

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Lidocaine paracervical block vs. no treatment										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	1[1]	RCT	Serious[a]	Not serious	Serious[b,c]	Not serious	26	24	Mean difference (95% CI): -1.02 (-2.08, 0.04) (p=0.06)	Low
Pain during IUD placement (10 cm VAS [mean])	2[1, 2]	RCT	Serious[a,d]	Not serious	Serious[b]	Not serious	68	70	Mean difference (95% CI): -0.78 (-1.37, -0.18) (p=0.01)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	2[1, 2]	RCT	Serious[a,d]	Not serious	Serious[b]	Not serious	68	70	Mean difference (95% CI): -0.55 (-1.36, 0.27) (p=0.19)	Low
Pain during tenaculum placement (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 4 (0-6) for lidocaine group vs. 7 (5-8) for comparison group; median difference: 3.0	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									(no pairwise test conducted)	
Pain during IUD placement (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 2 (0-5) for lidocaine group vs. 6 (3-7) for comparison; median difference: -4.0 (no pairwise test conducted)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 1 (0-4) for lidocaine group vs. 4 (1-6) for comparison group; median difference: -3.0	Low
Moderate or severe pain during tenaculum placement (%)	1[4]	RCT	Serious[g]	Not serious	Serious[b,c]	Not serious	47	49	Risk ratio (95% CI): 0.89 (0.55, 1.45) (p=0.65)	Low
Moderate or severe pain during IUD placement (%)	1[4]	RCT	Serious[g]	Not serious	Serious[b,c]	Not serious	47	49	Risk ratio (95% CI): 0.55 (0.37, 0.83) (p=0.004)*	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Need for Adjunctive Placement Measures										
Cervical dilation (%)	2[1, 3]	RCT	Serious[h]	Not serious	Serious[b,c]	Not serious	60	55	Risk ratio (95% CI): 0.92 (0.24, 3.49) (p=0.90)	Low
Placement Success										
Placement success (%)	2[1, 2]	RCT	Serious[i]	Not serious	Serious[c]	Not serious	68	70	Risk ratio (95% CI): 0.99 (0.96, 1.04) (p=0.80)	Low
Adverse Events										
Uterine perforation (%)	2[1, 3]	RCT	Serious[j]	Not serious	Very serious[c]	Not serious	60	55	0/60 vs. 0/55; Peto odds ratio (95% CI): not estimable due to 0 events observed	Very low
Vasovagal reaction (%)	2[1, 3]	RCT	Serious[j]	Not serious	Very serious[b,c]	Not serious	60	55	1/60 vs. 2/55; Peto odds ratio (95% CI): 0.46 (0.05, 4.56) (p=0.50)†	Very low
Lidocaine paracervical block vs. placebo/sham block										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 4 (0-6) for lidocaine group vs. 7 (4-9) for comparison group; median difference: -3.0 (no pairwise test conducted)	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Pain during IUD placement (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 2 (0-5) for lidocaine group vs. 6 (2-7) for comparison group; median difference: -4.0 (no pairwise test conducted)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[3]	RCT	Serious[e]	Not serious	Serious[c,f]	Not serious	34	31	Median (range): 1 (0-4) for lidocaine group vs. 4 (1-6) for comparison group; median difference: -3.0 (no pairwise test conducted)	Low
Pain during tenaculum placement (10 cm VAS [median])	1[5]	RCT	Serious[k]	Not serious	Serious[c,f]	Not serious	47	48	Median: 2.35 for lidocaine group vs. 6.00 for comparison group (p=0.001); median difference: -3.65*	Low
Pain during IUD placement (10 cm VAS [median])	1[5]	RCT	Serious[k]	Not serious	Serious[c,f]	Not serious	47	48	Median: 3.00 for lidocaine group vs. 7.15 for comparison group (p<0.001); median	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									difference: -4.15*	
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[5]	RCT	Serious[k]	Not serious	Serious[f,g]	Not serious	47	48	Median: 0.50 for lidocaine group vs. 2.90 for comparison group (p-value NR); median difference: -2.4	Low
Pain during tenaculum placement (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[c,f]	Not serious	33	31	Median (IQR): 1.5 (0.6-2.4) for lidocaine group vs. 1.0 (0.4-1.9) for comparison group (p=0.268); median difference: 0.5	Low
Pain during IUD placement (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[c,f]	Not serious	33	31	Median (IQR): 3.3 (1.0-5.6) for lidocaine group vs. 5.4 (3.3-7.5) for comparison group (p=0.002); median difference: -2.1*	Low
Highest level of pain after IUD placement	1[6]	RCT	Not serious	Not serious	Serious[c,f]	Not serious	33	31	Median (IQR): 1.2 (0.6-2.7) for lidocaine group vs. 2.7 (1.5-5.0) for comparison	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
and before clinic discharge (10 cm VAS [median])									group (p=0.005); median difference: -1.5*	
Need for Adjunctive Placement Measures										
Cervical dilation (%)	3[3, 5, 6]	RCT	Serious[k]	Not serious	Serious[b,c]	Not serious	114	109	Risk ratio (95% CI): 0.77 (0.22, 2.74) (p=0.69)	Low
Analgesia (%)	1[6]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	33	31	Risk ratio (95% CI): 0.47 (0.20, 1.10) (p=0.08)	Moderate
Placement Success										
Placement success (%)	2[5, 6]	RCT	Serious[k]	Not serious	Serious[c]	Not serious	80	79	Risk ratio (95% CI): 1.00 (0.97, 1.03) (p=1.00)	Low
Side Effects										
Tinnitus (%)	1[5]	RCT	Serious[k]	Not serious	Serious[c]	Not serious	47	48	Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vomiting (%)	1[6]	RCT	Not serious	Not serious	Serious[c]	Not serious	33	31	Peto odds ratio (95% CI): not estimable due to 0 events observed	Moderate
Dizziness (%)	1[6]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	33	31	Risk ratio (95% CI): 1.17 (0.53, 2.59) (p=0.69)	Moderate
Adverse Events										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Uterine perforation (%)	2[3,5]	RCT	Serious[l]	Not serious	Very serious[c]	Not serious	81	78	0/81 vs. 0/78; Peto odds ratio (95% CI): not estimable due to 0 events observed	Very low
Vasovagal reaction (%)	1[3]	RCT	Serious[e]	Not serious	Very serious[b,c]	Not serious	34	30	1/34 vs. 2/30; Peto odds ratio (95% CI): 0.44 (0.04, 4.41) (p=0.49)	Very low
Patient Satisfaction with Procedure										
Satisfied with IUD placement procedure (%)	1[5]	RCT	Serious[k]	Not serious	Serious[c]	Not serious	47	48	Risk ratio (95% CI): 1.00 (0.88, 1.13) (p=0.98)	Low
Would recommend an IUD to a friend (%)	1[5]	RCT	Serious[k]	Not serious	Serious[c]	Not serious	47	48	Risk ratio (95% CI): 1.07 (0.93, 1.24) (p=0.36)	Low
Would choose the same pain control method for a future IUD (%)	1[6]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	33	31	Risk ratio (95% CI): 1.25 (0.79, 1.98) (p=0.33)	Moderate
Would recommend pain control method to	1[6]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	33	31	Risk ratio (95% CI): 1.47 (0.99, 2.17) (p=0.05)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
a friend for IUD placement (%)										
Lidocaine intracervical block vs. no treatment										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	1[7]	RCT	Not serious	Not serious	Serious[b]	Not serious	99	101	Mean difference (95% CI): -2.00 (-2.64, -1.36) (p<0.00001)*	Moderate
Pain during IUD placement (10 cm VAS [mean])	1[7]	RCT	Not serious	Not serious	Serious[b]	Not serious	99	101	Mean difference (95% CI): -1.50 (-2.28, -0.72) (p=0.0002)*	Moderate
Provider Ease of Placement										
"Usual" placement (%)	1[7]	RCT	Not serious	Not serious	Serious[b]	Not serious	99	102	Risk ratio (95% CI): 1.13 (1.02, 1.25) (p=0.02)	Moderate
Need for Adjunctive Placement Measures										
Cervical dilation (%)	1[7]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	99	102	Risk ratio (95% CI): 0.43 (0.16, 1.17) (p=0.10)	Moderate
Placement Success										
Placement Success (%)	1[7]	RCT	Not serious	Not serious	Serious[c]	Not serious	99	102	Risk ratio (95% CI): 1.01 (0.98, 1.04) (p=0.49)	Moderate
Adverse Events										
Uterine perforation (%)	1[7]	RCT	Not serious	Not serious	Very serious[c]	Not serious	99	102	0/99 vs. 0/102; Peto odds ratio (95% CI): not	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									estimable due to 0 events observed	
Vasovagal reaction (%)	1[7]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	99	102	1/99 vs. 7/102; Peto odds ratio (95% CI): 0.22 (0.05, 0.89) (p=0.03)*	Moderate
Lidocaine intracervical block vs. placebo/sham block										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	1[7]	RCT	Not serious	Not serious	Serious[b]	Not serious	99	100	Mean difference (95% CI): -2.60 (-3.24, -1.96) (p<0.00001)*	Moderate
Pain during IUD placement (10 cm VAS [mean])	1[7]	RCT	Not serious	Not serious	Serious[b]	Not serious	99	100	Mean difference (95% CI): -2.30 (-2.98, -1.62) (p<0.00001)*	Moderate
Provider Ease of Placement										
"Usual" placement (%)	1[7]	RCT	Not serious	Not serious	Not serious	Not serious	99	101	Risk ratio (95% CI): 1.08 (0.99, 1.18) (p=0.10)	High
Need for Adjunctive Placement Measures										
Cervical dilation (%)	1[7]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	99	101	Risk ratio (95% CI): 0.57 (0.20, 1.63) (p=0.29)	Moderate
Placement Success										
Placement Success (%)	1[7]	RCT	Not serious	Not serious	Serious[c]	Not serious	99	101	Risk ratio (95% CI): 1.01 (0.98, 1.04) (p=0.48)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Adverse Events										
Uterine perforation (%)	1[7]	RCT	Not serious	Not serious	Very serious[c]	Not serious	99	101	0/99 vs. 0/101; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vasovagal reaction (%)	1[7]	RCT	Not serious	Not serious	Serious[b,c]	Not serious	99	101	1/99 vs. 7/101; Peto odds ratio (95% CI): 0.22 (0.05, 0.88) (p=0.03)*	Moderate

CI, confidence interval; IQR, interquartile range; IUD, intrauterine device; NR, not reported; OR, odds ratio; RCT, randomized clinical trial; VAS, visual analog score

Footnotes

*Effect was statistically significant and clinically relevant.

†One study had non-estimable peto OR; peto OR represents data from one study.

[a]Risk of bias is considered serious due to lack of information on the allocation concealment processes in one study.

[b]Imprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

[c]Imprecision is considered serious due to the small sample size.

[d]Risk of bias is considered serious due to the outcome being self-reported by participants who were probably aware of their assigned intervention in one study.

[e]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes in the study.

[f]Imprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

[g]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes and outcome being self-reported by participants who were probably aware of their assigned intervention.

[h]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes in two studies and outcome assessors were aware of the assigned intervention received by study participants in one study.

[i]Risk of bias is considered serious due to lack of information on allocation concealment in one study and outcome being reported by outcome assessors were aware of the assigned intervention received by study participants in two studies.

[j]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes in two studies and outcome assessors were aware of the assigned intervention received by study participants in one study.

[k]Risk of bias is considered serious due to lack of information on allocation concealment processes in one study.

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2.3.2 Topical lidocaine

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Topical lidocaine vs. placebo/no treatment										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	4[1-4]	RCT	Not serious	Serious[a]	Serious[d]	Not serious	201	201	Mean difference (95% CI): -1.69 (-2.53, -0.85) (p<0.0001)*	Low
Pain during IUD placement (10 cm VAS [mean])	8[1-8]	RCT	Not serious	Serious[a]	Serious[d]	Not serious	540	541	Mean difference (95% CI): -0.97 (-1.69, -0.24) (p=0.009)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	2[2, 3]	RCT	Not serious	Not serious	Not serious	Not serious	110	110	Mean difference (95% CI): -0.65 (-0.94, -0.36) (p<0.0001)	High
Moderate or severe pain during tenaculum placement (%)	3[b,9, 10]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	166	111	Risk ratio (95% CI): 0.62 (0.36, 1.05) (p=0.08)	Low
Moderate or severe pain during	3[b,9, 10]	RCT	Serious[c]	Serious[a]	Serious[d]	Not serious	166	112	Risk ratio (95% CI): 0.76 (0.50, 1.18) (p=0.22)	Very low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
IUD placement (%)										
Highest level of pain after IUD placement and before clinic discharge (% with 10 cm VAS score ≥4)	1[10]	RCT	Not serious	Not serious	Serious[d]	Not serious	62	62	Risk ratio (95% CI): 0.64 (0.26, 1.53) (p=0.31)	Moderate
Pain during tenaculum placement (10 cm VAS [median])	1[11]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	30	29	Median (IQR): 3.2 (1.8-5.4) vs. 5.6 (2.6-7.5) (p=0.02); median difference: -2.4*	Moderate
Pain during IUD placement (10 cm VAS [median])	1[11]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	30	29	Median (IQR): 6.1 (5.3-7.1) vs. 6.9 (6.3-8.0) (p=0.06); median difference: -0.8	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[11]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	30	29	Median (IQR): 2.9 (1.1-5.7) vs. 3.8 (1.8-6.2) (p=0.28); median difference: -0.9	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Pain during tenaculum placement (10 cm VAS [median])	1[12]	RCT	Not serious	Not serious	Serious[f]	Not serious	60	60	Median (IQR): 2 (2-3) vs. 4 (3-6) (p=0.0001); median difference: -2.0*	Moderate
Pain during IUD placement (10 cm VAS [median])	1[12]	RCT	Not serious	Not serious	Serious[f]	Not serious	60	60	Median (IQR): 3 (2-3) vs. 6.5 (4-8) (p=0.0001); median difference: -3.5*	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[12]	RCT	Not serious	Not serious	Serious[f]	Not serious	60	60	Median (IQR): 2 (1-2) vs. 3.5 (2-6) (p=0.0001); median difference: -1.5*	Moderate
Pain during tenaculum placement (10-point scale [median])	1[13]	RCT	Not serious	Not serious	Serious[f]	Not serious	100	99	Median (range): 4 (0-10) vs. 4 (0-10) (p=0.15); median difference: 0.0	Moderate
Pain during IUD placement (10-point scale [median])	1[13]	RCT	Not serious	Not serious	Serious[f]	Not serious	100	99	Median (range): 5 (0-10) vs. 6 (0-10) (p=0.16); median difference: -1.0	Moderate
Pain during tenaculum	1[6]	RCT	Not serious	Not serious	Serious[f]	Not serious	108	107	Median (range): 3.0 (0-8.6) vs. 3.8	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
placement (10 cm VAS [median])									(0-8.4) (p=0.15); median difference: -0.8	
Provider Ease of Placement										
Provider ease of placement (10 cm VAS [mean])	3[1, 3, 12]	RCT	Not serious	Serious[a]	Serious[d]	Not serious	175	175	Mean difference (95% CI): -1.48 (-2.50, -0.45) (p=0.005)	Low
Easy placement (%)	1[11]	RCT	Not serious	Not serious	Serious[d,e]	Not serious	30	28	Risk ratio (95% CI): 1.35 (0.99, 1.84) (p=0.06)	Moderate
Provider ease of placement (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[f]	Not serious	108	107	Median (range): 0.9 (0.1-9.8) vs. 0.9 (0-9.6) (p=0.84); median difference: 0.0	Moderate
Need for Adjunctive Placement Measures										
Cervical dilation (%)	2[7, 11]	RCT	Not serious	Serious[a]	Serious[d,e]	Not serious	130	129	Risk ratio (95% CI): 0.38 (0.04, 3.62) (p=0.40)	Low
Analgesia (%)	2[10, 12]	RCT	Not serious	Not serious	Serious[d]	Not serious	122	122	1/122 vs. 6/122; Peto odds ratio (95% CI): 0.22 (0.05, 1.02) (p=0.05)†	Moderate
Local anesthesia (%)	1[7]	RCT	Not serious	Not serious	Serious[d,e]	Not serious	100	100	1/100 vs. 1/100; Peto odds ratio (95% CI): 1.00 (0.06, 16.10) (p=1.00)	Moderate
Placement Success										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Placement success (%)	8[1, 2, 5-7, 10, 11, 13]	RCT	Not serious	Not serious	Not serious	Not serious	587	585	Risk ratio (95% CI): 0.99 (0.99, 1.01) (p=0.56)	High
Adverse Events										
Uterine perforation (%)	5[1, 3, 7, 10, 12]	RCT	Not serious	Not serious	Very serious[d,e]	Not serious	337	337	1/337 vs. 0/337; Peto odds ratio (95% CI): 7.39 (0.15, 372.38) (p=0.32)[§]	Low
Vasovagal reaction (%)	4[1, 3, 10, 12]	RCT	Not serious	Not serious	Very serious[d,e]	Not serious	237	237	1/237 vs. 2/237; Peto odds ratio (95% CI): 0.51 (0.05, 4.99) (p=0.56)[¶]	Low
Patient Satisfaction with Procedure										
"Very satisfied" with IUD placement (%)	1[11]	RCT	Not serious	Not serious	Serious[d,e]	Not serious	30	28	57% vs. 50%; Risk ratio (95% CI): 1.13 (0.70, 1.84) (p=0.61)	Moderate
How likely to recommend IUD placement to someone wanting to use the method (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[f]	Not serious	108	107	Median (range): 8.7 (3.3-10) vs. 8.3 (9-10) (p=0.64); median difference: 0.4	Moderate

CI, confidence interval; IQR, interquartile range; IUD, intrauterine device; NR, not reported; OR, odds ratio; RCT, randomized clinical trial; VAS, visual analog score

Footnotes

*Effect was statistically significant and clinically relevant.

[†]One study had non-estimable peto OR; peto OR represents data from one study.

[§]Four studies had non-estimable peto ORs; peto OR represents data from one study.

[¶]Three studies had non-estimable peto ORs; peto OR represents data from one study.

[a]Inconsistency is considered serious due to varying results among studies.

[b]One study is included twice in the analysis because it examined two interventions.

[c]Risk of bias is considered serious due to lack of information on randomization and allocation concealment processes in one study which is included twice in the analysis.

[d]Imprecision is considered serious or very serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

[e]Imprecision is considered serious or very serious due to the small sample size.

[f]Imprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

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2.3.3 Intrauterine instillation

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Intrauterine instillation vs. placebo										
Patient Pain										
Pain during IUD placement (patient reported) (10 cm VAS or 9-point scale [mean])	3[a,1, 2]	RCT	Serious[b]	Not serious	Not serious	Not serious	98	58	Standardized mean difference (95% CI): -0.23 (-0.56, 0.10) (p=0.18)	Moderate
Pain during IUD placement (provider reported) (3-point scale [mean])	2[a,1]	RCT	Serious[b]	Not serious	Not serious	Not serious	78	38	Mean difference (95% CI): 0.07 (-0.18, 0.33) (p=0.57)	Moderate
Pain during tenaculum placement (10 cm VAS [median])	1[3]	RCT	Not serious	Not serious	Serious[c,d]	Not serious	41	40	Median (IQR): 2.2 (0.9-3.4) vs. 2.4 (0.3-4.5) (p=0.487); median difference: -0.4	Moderate
Pain during IUD placement (10 cm VAS [median])	1[3]	RCT	Not serious	Not serious	Serious[c,d]	Not serious	41	40	Median (IQR): 4.8 (3.1-5.8) vs. 5.9 (3.3-7.5) (p=0.062); median difference: -1.1	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	1[4]	RCT	Not serious	Not serious	Serious[e]	Not serious	106	103	Mean difference (95% CI): -1.59 (-2.28, -0.90) (p<0.00001)*	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[3]	RCT	Not serious	Not serious	Serious[c,d]	Not serious	41	40	Median (IQR): 1.3 (0.5-2.5) vs. 1.3 (0.6-3.7) (p=0.545); median difference: 0.0	Moderate
Provider Ease of Placement										
Easy placement (%)	2[a,1]	RCT	Serious[b]	Not serious	Not serious	Not serious	78	38	97% vs. 95%; Risk ratio (95% CI): 1.03 (0.95, 1.12) (p=0.51)	Moderate
Need for Adjunctive Placement Measures										
Analgesia (%)	1[4]	RCT	Not serious	Not serious	Serious[e]	Not serious	110	108	15% vs 31%; Risk ratio (95% CI): 0.51 (0.30, 0.85) (p=0.01)*	High
Placement Success										
Placement success (%)	5[a,1-4]	RCT	Not serious	Not serious	Not serious	Not serious	249	210	98% vs 96%; Risk ratio (95% CI): 1.03 (0.99, 1.07) (p=0.17)	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Patient Satisfaction with Procedure										
Patient satisfaction (5-point scale [mean])	2[a,1]	RCT	Serious[b]	Not serious	Serious[c]	Not serious	78	38	Mean difference (95% CI): -0.09 (-0.44, 0.26) (p=0.62)	Low
Would choose an IUD for contraception again (%)	1[3]	RCT	Not serious	Not serious	Serious[c]	Not serious	41	40	95% vs. 93%; Risk ratio (95% CI): 1.03 (0.92, 1.15) (p=0.63)	Moderate
Would recommend an IUD to a friend (%)	1[3]	RCT	Not serious	Not serious	Serious[c]	Not serious	41	40	98% vs. 95%; Risk ratio (95% CI): 1.03 (0.94, 1.12) (p=0.54)	Moderate

CI, confidence interval; IQR, interquartile range; IUD, intrauterine device; RCT, randomized clinical trial; VAS, visual analog score

Footnotes

*Effect was statistically significant and clinically relevant.

[a]One study is included twice in the analysis because it examined two interventions.

[b]Risk of bias is considered serious due to lack of information on allocation concealment processes in one study which is included twice in the analysis.

[c]Imprecision is considered serious due to the small sample size.

[d]Imprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

[e]Imprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

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2.4 Provision of medications for intrauterine device (IUD) placement: Analgesics

Systematic review question: Among patients receiving an interval IUD (i.e., placement outside the postabortion or postpartum period), does the use of analgesics affect patient or provider outcomes compared with placebo or no treatment? This table is based on Zapata LB, Nguyen AT, Snyder E, Napp K, Ti A, Whiteman MK, Curtis KM. Analgesics for intrauterine device placement. Cochrane Database of Systematic Reviews 2024: In preparation.

Methods: All effects presented below are from pooled meta-analysis, except when the number of studies was one.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
NSAIDs vs. placebo										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	2[1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	114	107	Mean difference (95% CI): -0.24 (-0.70, 0.22) (p=0.31)	High
Pain during IUD placement (patient-reported) (10 cm VAS or scale [mean])	5[1-5]	RCT	Serious[a]	Serious[b]	Serious[c]	Not serious	224	215	Mean difference (95% CI): -0.95 (-1.76, -0.14) (p=0.02)	Very low
Pain during IUD placement (provider-reported) (10 cm VAS [mean])	1[5]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	40	38	Mean difference (95% CI): -0.11 (-0.37, 0.15) (p=0.40)	Low
Highest level of pain after IUD placement and before clinic discharge	2[2, 3]	RCT	Not serious	Not serious	Not serious	Not serious	105	106	Mean difference (95% CI): -0.52 (-0.84, -0.20) (p=0.001)	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
(10 cm VAS [mean])										
Pain during tenaculum placement (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	33	34	Median (IQR): 2.5 (1.1-6.4) for NSAID group vs. 3.9 (2.6-5.7) for placebo group (p=0.36); median difference: -1.9	Moderate
Pain during IUD placement (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	33	34	Median (IQR): 3.6 (1.5-6.3) for NSAID group vs. 5.2 (1.2-7.4) for placebo group (p=0.99); median difference: -1.6	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[6]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	33	34	Median (IQR): 3.3 (0-1.3) for NSAID group vs. 2.2 (0.8-3.9) for placebo group (p<0.001); median difference: 1.1	Moderate
Pain during tenaculum placement (10 cm VAS [median])	1[7]	RCT	Not serious	Not serious	Serious[f]	Not serious	58	60	Median: 3.7 for NSAID group vs. 3.2 for placebo group (p=0.97); median difference: 0.5	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Pain during IUD placement (10 cm VAS [median])	1[7]	RCT	Not serious	Not serious	Serious[f]	Not serious	58	60	Median: 6.9 for NSAID group vs. 6.6 for placebo group (p=0.89); median difference: 0.3	Moderate
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[7]	RCT	Not serious	Not serious	Serious[f]	Not serious	58	60	Median: 1.7 for NSAID group vs. 2.6 for placebo group (p=0.01); median difference: -0.9	Moderate
Pain during tenaculum placement (10 cm VAS [median])	1[8]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	48	46	Median (IQR): 2 (1-3) for NSAID group vs. 4 (3-5) for placebo group (p<0.001); median difference: -2.0*	Moderate
Pain during IUD placement (10 cm VAS [median])	1[8]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	48	46	Median (IQR): 2.3 (2-3) for NSAID group vs. 5 (3-7) for placebo group (p<0.001); median difference: -2.7*	Moderate
Highest level of pain after IUD placement and before	1[8]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	48	46	Median (IQR): 1 (1-1.5) for NSAID group vs. 2 (1-2) for placebo group (p<0.001); median difference: -1.0	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
clinic discharge (10 cm VAS [median])										
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median])	1[9]	RCT	Not serious	Not serious	Serious[f]	Not serious	65	65	Median (IQR): 4 (1.5-6) for NSAID group vs. 4 (2-6) for placebo group (p=0.873); median difference: 0.0	Moderate
Pain during IUD placement (10-point scale [median])	1[10]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	27	28	Median: 3.3 for NSAID group vs. 2.5 for placebo group (p-value NR); median difference: 0.8	Moderate
Pain during IUD placement (10 cm VAS [median])	1[11]	RCT	Not serious	Not serious	Serious[f]	Not serious	1011	1008	Median: 1.0 for NSAID group vs. 1.0 for placebo group (p-value NR); median difference: 0.0	Moderate
Highest level of pain after IUD placement and before clinic discharge	1[12]	RCT	Not serious	Not serious	Serious[f]	Not serious	101	101	Median (range): 3.8 (0-10) for NSAID group vs. 4.2 (0-10) for placebo group (p=0.50); median difference: -0.4	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
(10 cm VAS [median])										
Provider Ease of Placement										
Provider ease of placement (10 cm VAS [mean])	2[2, 8]	RCT	Not serious	Serious[b]	Serious[c]	Not serious	118	116	Mean difference (95% CI): -0.90 (-2.34, 0.54) (p=0.22)	Low
Moderate or severe resistance with placement (%)	1[1]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	44	37	Risk ratio (95% CI): 7.57 (1.00, 57.01), p=0.05	Moderate
Easy placement (%)	1[5]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	40	38	Risk ratio (95% CI): 1.00 (0.90, 1.11) (p=0.96)	Low
Need for Adjunctive Placement Measures										
Cervical dilation (%)	4[1, 3, 6, 7]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	170	167	Risk ratio (95% CI): 0.91 (0.39, 2.12) (p=0.83)	Moderate
Analgesia (%)	4[2, 6-8]	RCT	Not serious	Not serious	Not serious	Not serious	209	208	Risk ratio (95% CI): 0.55 (0.40, 0.74) (p=0.0001)*	High
Placement Success										
Placement success (%)	11[1-9, 11, 12]	RCT	Not serious	Not serious	Not serious	Not serious	1540	1539	Risk ratio (95% CI): 1.00 (1.00, 1.01) (p=0.37)	Moderate
Side Effects										
Nausea (%)	3[4, 6, 7]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	126	128	Risk ratio (95% CI): 0.48 (0.20, 1.14) (p=0.10)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Vomiting (%)	3[4, 6, 7]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	126	128	Peto odds ratio (95% CI): 0.14 (0.01, 2.23) (p=0.16)[†]	Moderate
Dizziness (%)	2[4, 6]	RCT	Serious[g]	Not serious	Serious[c,e]	Not serious	68	68	Peto odds ratio (95% CI): 0.67 (0.11, 4.12) (p=0.67)*	Low
Drowsiness (%)	1[6]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	33	34	Risk ratio (95% CI): 1.03 (0.07, 15.80) (p=0.98)	Moderate
Adverse Events										
Uterine perforation (%)	2[2, 8]	RCT	Not serious	Not serious	Very serious[c,e]	Not serious	118	116	0/118 vs. 0/116; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vasovagal reaction (%)	3[2, 7, 8]	RCT	Not serious	Not serious	Very serious[c,e]	Not serious	176	176	2/176 vs. 3/176; Peto odds ratio (95% CI): 0.68 (0.11, 4.08) (p=0.68)[†]	Low
Patient Satisfaction with Placement										
Patient satisfaction (10 cm VAS or 5-point scale [mean])	3[2, 5, 8]	RCT	Not serious	Serious[b]	Not serious	Not serious	158	154	Standardized mean difference (95% CI): 0.54 (-0.05, 1.14), p=0.07	Moderate
Very satisfied (%)	1[6]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	33	33	Risk ratio (95% CI): 1.13 (0.70, 1.80) (p=0.62)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Unpleasant /very unpleasant (%)	1[4]	RCT	Serious[g]	Not serious	Serious[e]	Not serious	34	34	Risk ratio (95% CI): 0.17 (0.07, 0.38) (p<0.0001)*	Low
Patient satisfaction (10 cm VAS [median])	1[7]	RCT	Not serious	Not serious	Serious[e,f]	Not serious	58	60	Median (IQR): 9.2 (8.3-9.9) for NSAID group vs. 9.1 (8.2-9.8) for placebo group (p=0.56); median difference: 0.1	Moderate
NSAID + lidocaine vs. placebo										
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean])	1[13]	RCT	Not serious	Not serious	Serious[e]	Not serious	45	45	Mean difference (95% CI): -0.67 (-1.10, -0.24), p=0.002	Moderate
Pain during IUD placement (patient-reported) (10 cm VAS [mean])	2[5, 13]	RCT	Serious[d]	Not serious	Not serious	Not serious	84	83	Mean difference (95% CI): -0.72 (-1.14, -0.29) (p=0.001)	Moderate
Pain during IUD placement (provider-reported) (10 cm VAS [mean])	1[5]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	39	38	Mean difference (95% CI): 0.18 (-0.08, 0.44) (p=0.17)	Low
Provider Ease of Placement										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Provider ease of placement (10 cm VAS [mean])	1[13]	RCT	Not serious	Not serious	Serious[e]	Not serious	45	45	Mean difference (95% CI): -0.22 (-0.95, 0.51) (p=0.56)	Moderate
Easy placement (%)	1[5]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	39	38	Risk ratio (95% CI): 1.03 (0.94, 1.13) (p=0.54)	Low
Placement Success										
Placement success (%)	2[5, 13]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	84	84	Risk ratio (95% CI): 1.01 (0.97, 1.04), p=0.71	Low
Adverse Events										
Uterine perforation (%)	1[13]	RCT	Not serious	Not serious	Very serious[e]	Not serious	45	45	0/45 vs. 0/45; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vasovagal reaction (%)	1[13]	RCT	Not serious	Not serious	Very serious[d,e]	Not serious	45	45	1/45 vs. 2/45; Peto odds ratio (95% CI): 0.51 (0.05, 4.99) (p=0.56)	Low
Patient Satisfaction with Placement										
Patient satisfaction (5-point scale [mean])	1[5]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	39	38	Mean difference (95% CI): -0.04 (-0.43, 0.35) (p=0.84)	Low
NSAID + muscle relaxant vs. placebo										
Patient Pain										
Pain during IUD	1[14]	RCT	Serious[h]	Not serious	Serious[c,e]	Not serious	31	25	Mean difference (95% CI): -2.00 (-	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
placement (10 cm VAS [mean])									2.77, -1.23) (p<0.00001)*	
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	1[14]	RCT	Serious[h]	Not serious	Serious[e]	Not serious	31	25	Mean difference (95% CI): -0.73 (-1.15, -0.31) (p=0.0006)	Low
Placement Success										
Placement success (%)	1[14]	RCT	Serious[h]	Not serious	Serious[e]	Not serious	31	25	Risk ratio (95% CI): 1.00 (0.93, 1.07) (p=1.00)	Low
Tramadol vs. placebo										
Patient Pain										
Pain during IUD placement (10 cm VAS [mean])	2[4, 15]	RCT	Serious[i]	Serious[b]	Serious[c]	Not serious	56	66	Mean difference (95% CI): -1.49 (-3.71, 0.73) (p=0.19)	Very low
Provider Ease of Placement										
Provider ease of placement (scale not described [mean])	1[15]	RCT	Serious[j]	Not serious	Serious[c,e]	Not serious	22	32	Mean difference (95% CI): -1.80 (-2.71, -0.89) (p=0.0001)*	Low
Placement Success										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Placement success (%)	2[4, 15]	RCT	Serious[i]	Not serious	Serious[e]	Not serious	56	66	Risk ratio (95% CI): 1.00 (0.96, 1.05) (p=1.00)	Low
Side Effects										
Nausea (%)	1[4]	RCT	Serious[g]	Not serious	Serious[e]	Not serious	34	34	0/34 vs. 0/34; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Vomiting (%)	1[4]	RCT	Serious[g]	Not serious	Serious[e]	Not serious	34	34	0/34 vs. 0/34; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Dizziness (%)	1[4]	RCT	Serious[g]	Not serious	Serious[e]	Not serious	34	34	0/34 vs. 0/34; Peto odds ratio (95% CI): not estimable due to 0 events observed	Low
Adverse Events										
Vasovagal reaction (%)	1[15]	RCT	Not serious	Not serious	Very serious[c,e]	Not serious	22	32	1/22 vs. 0/32; Peto odds ratio (95% CI): (0.22, 628.58) (p=0.23)	Low
Patient Satisfaction with Placement										
Unpleasant /very unpleasant (%)	1[4]	RCT	Serious[g]	Not serious	Serious[e]	Not serious	35	34	6% of tramadol group vs. 88% of placebo group; Risk ratio (95% CI): 0.06 (0.02, 0.25) (p<0.0001)*	Low
Acetaminophen vs. placebo										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Patient Pain										
Pain during IUD placement (10 cm VAS [mean])	1[16]	RCT	Serious[k]	Not serious	Serious[e]	Not serious	30	46	Mean difference (95% CI): -0.64 (-1.14, -0.14) (p=0.01)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [mean])	1[16]	RCT	Serious[k]	Not serious	Serious[e]	Not serious	30	46	Mean difference (95% CI): -0.83 (-1.26, -0.40) (p=0.0001)	Low
Placement Success										
Placement success (%)	1[16]	RCT	Serious[j]	Not serious	Serious[e]	Not serious	30	46	Risk ratio (95% CI): 1.00 (0.95, 1.06) (p=1.00)	Low
Nitrous Oxide vs. placebo										
Patient Pain										
Highest level of pain after IUD placement and before clinic (10 cm VAS [mean])	1[17]	RCT	Not serious	Not serious	Serious[e]	Not serious	40	40	Mean difference (95% CI): -0.10 (-1.11, 0.91) (p=0.85)	Moderate
Provider Ease of Placement										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Provider ease of placement (10 cm VAS [mean])	1[17]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	40	40	Mean difference (95% CI): 0.74 (-0.24, 1.72), p=0.14	Moderate
Placement Success										
Placement success (%)	1[17]	RCT	Not serious	Not serious	Serious[e]	Not serious	40	40	Risk ratio (95% CI): 0.98 (0.91, 1.04) (p=0.48)	Moderate
Side Effects										
Nausea (%)	1[17]	RCT	Not serious	Not serious	Serious[e]	Not serious	40	40	0/40 vs. 5/40; Peto OR (95% CI): 0.12 (0.02, 0.74) (p=0.02)*	Moderate
Dizziness (%)	1[17]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	40	40	3/40 vs. 0/40; Peto OR (95% CI): 7.78 (0.79, 77.04) (p=0.08)	Moderate
Patient Satisfaction with Placement										
Satisfaction with pain management during IUD placement (10 cm VAS [mean])	1[17]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	40	40	Mean difference (95% CI): 0.57 (-0.72, 1.86) (p=0.39)	Moderate
Satisfied or very satisfied with pain management during	1[17]	RCT	Not serious	Not serious	Serious[c,e]	Not serious	40	40	Risk ratio (95% CI): 1.59 (1.04, 2.42) (p=0.03)*	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
IUD placement (%)										

CI, confidence interval; IQR, interquartile range; IUD, intrauterine device; MD, mean difference; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; RCT, randomized clinical trial; RR, risk ratio; SMD, standardized mean difference; VAS, visual analog score

Footnotes

*Effect was statistically significant and clinically relevant.

[†]Two studies had non-estimable peto ORs; peto OR represents data from one study.

[§]One study had non-estimable peto OR; peto OR represents data from one study.

[a]Risk of bias is considered serious due to lack of information on allocation concealment processes in two studies and outcome assessors were aware of the assigned intervention received by study participants in one study.

[b]Inconsistency is considered serious due to varying results among studies.

[c]Imprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

[d]Risk of bias is considered serious due to lack of information on allocation concealment processes in one study.

[e]Imprecision is considered serious or very serious due to the small sample size.

[f]Imprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

[g]Risk of bias is considered serious due to lack of information on allocation concealment processes and outcome assessors were aware of the assigned intervention received by study participants in one study.

[h]Risk of bias is considered serious due to lack of information on allocation concealment processes in one study.

[i]Risk of bias is considered serious due to lack of information on allocation concealment processes in one study and outcome assessors were aware of the assigned intervention received by study participants in two studies.

[j]Risk of bias is considered serious due to outcome assessors were aware of the assigned intervention received by study participants in one study.

[k]Risk of bias is considered serious due to the outcome being self-reported by participants who were probably aware of their assigned intervention in one study.

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2.5 Provision of medications for intrauterine device (IUD) placement: Smooth muscle relaxants

Systematic review question: Among patients receiving an interval IUD (i.e., placement outside the postabortion or postpartum period), does the use of smooth muscle relaxants affect patient or provider outcomes compared with placebo or no treatment? This table is based on Snyder E, Krishna G, Zapata LB, Nguyen AT, Whiteman MK, Curtis KM. Smooth muscle relaxants for intrauterine device placement: A systematic review. Contraception 2024: In preparation.

Methods: All effects presented below are from individual estimates; no meta-analysis was conducted.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Topical smooth muscle relaxants vs. placebo										
Patient Pain										
Pain during tenac-ulum place-ment	3[a,1-3]	RCT	Not serious	Serious[b]	Not serious	Not serious	75	73	No significant difference in pain scores for 2 studies; significantly lower median pain VAS scores for treatment group vs. placebo group in 1 study (2 vs. 4 cm, p<0.0001)*	Moderate
Pain during IUD place-ment	3[a,1-3]	RCT	Not serious	Serious[b]	Not serious	Not serious	75	73	No significant difference in pain scores for 2 studies; significantly lower median pain VAS scores for treatment group vs. placebo group in 1 study (3 vs. 5.5 cm, p<0.0001)*	Moderate
Highest level of pain after IUD place-ment and before clinic discharge	3[a,1-3]	RCT	Not serious	Serious[b]	Not serious	Not serious	75	73	No significant difference in pain scores for 2 studies; significantly lower median pain VAS scores for treatment group vs. placebo group in 1 study (2 vs. 3.5 cm, p=0.009)*	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Provider Ease of Placement										
Easy placement	3[a,1-3]	RCT	Not serious	Serious[b]	Not serious	Not serious	75	73	No significant difference in ease of placement for 2 studies; higher mean ease of placement VAS scores for treatment group vs. placebo group in 1 study (6.94±1.15 vs. 4.74±1.38, p<0.0001)*	Moderate
Need for Adjunctive Placement Measures										
Cervical dilation	2[a,1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	25	23	No significant difference between groups	High
Local anesthetic	2[a,1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	25	23	1 participant had paracervical block but study did not specify which group; no participants received anesthetic in other study	High
Placement Success										
Placement success	3[a,1-3]	RCT	Not serious	Not serious	Not serious	Not serious	75	73	No significant difference (all participants had successful placements in both groups)	High
Patient Satisfaction with Procedure										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Patient satis-faction	3[a,1-3]	RCT	Not serious	Serious[b]	Not serious	Not serious	75	73	No significant difference in 2 studies; 1 study had significantly higher satisfaction scores in treatment group vs. placebo group (92% vs. 74%, p=0.003)	Moderate
Side Effects										
Nausea	2[a,1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	25	23	No significant difference between groups	High
Vomiting	2[a,1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	25	23	No significant difference between groups	High
Diarrhea	2[a,1, 2]	RCT	Not serious	Not serious	Not serious	Not serious	25	23	No significant difference between groups	High
Adverse Events										
Vasovagal reaction	2[a,1, 2]	RCT	Not serious	Not serious	Serious[c]	Not serious	25	23	1 study had 2 participants in treatment group experience vasovagal reactions; none reported in other study	Moderate
Uterine perfor-ation	1[3]	RCT	Not serious	Not serious	Serious[c]	Not serious	50	50	None reported	Moderate
Drotaverine+mefenamic acid vs. placebo										
Patient Pain										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Pain during IUD place-ment	1[4]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	31	25	Treatment group had lower mean±SD pain scores vs. placebo group (2.32±1.137 vs. 4.32±1.676, p=0.001)*	Low
Highest level of pain after IUD place-ment and before clinic discharge	1[4]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	31	25	Treatment group had lower mean±SD pain scores vs. placebo group (1.28±0.59 vs. 2.01±0.93, p=0.001)	Low
Placement Success										
Place-ment success	1[4]	RCT	Serious[d]	Not serious	Serious[e]	Not serious	31	25	No difference (all participants had successful placements in both groups)	Low
Isonicotinic acid hydrazide (INH) vs. placebo										
Patient Pain										
Pain during tenac-ulum place-ment	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Lower median pain VAS scores in treatment groups vs. placebo groups (2 vs. 4 cm, p<0.01; 3 vs. 5 cm, p=0.0001)*	High
Pain during IUD place-ment	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Lower mean pain VAS scores in treatment groups vs. placebo groups (3.9 vs. 5.3 cm, p<0.01;	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									3.97 vs. 6.42 cm, p=0.0001)*	
Highest level of pain after IUD place-ment and before clinic discharge	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Lower median pain VAS scores in treatment groups vs. placebo groups (2 vs. 3 cm, p<0.01; 2 vs. 4 cm, p=0.0001)*	High
Provider Ease of Placement										
Easy place-ment	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Lower median ease of insertion (indicating easier insertions) VAS scores in treatment groups vs. placebo groups (3 vs. 5 cm, p<0.01; 3 vs. 6 cm, p=0.0001)*	High
Need for Adjunctive Placement Measures										
Cervical dilation	2[a,5, 6]	RCT	Not serious	Very serious[f]	Not serious	Not serious	210	210	More participants in treatment group required cervical dilation vs. placebo group in first study (72% vs. 42%, p-value not reported); Less participants in treatment group required dilation vs. placebo group in	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									second study (7.3% vs. 16.5%, p=0.01)	
Analgesia	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Fewer participants in treatment groups requested analgesia vs. placebo groups (4.5% vs. 24.5%; 7% vs. 25%, p-values not reported)	High
Placement Success										
Place-ment success	2[a,5, 6]	RCT	Not serious	Serious[b]	Not serious	Not serious	210	210	First study: no difference (all participants had successful placements); Second study: 2 failed placements in treatment group and 4 failed placements in placebo group (p=0.594)	Moderate
Patient Satisfaction with Procedure										
Patient satis-faction	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	Higher mean satisfaction VAS scores in treatment groups vs. placebo groups (8.1±0.6 vs. 5.5±0.7, p<0.01; data not reported, p=0.0001)	High
Side Effects										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Nausea	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	No significant difference between groups	High
Vomiting	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	No significant difference between groups	High
Diarrhea	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	No significant difference between groups	High
Abdom-inal pain/ cramping	2[a,5, 6]	RCT	Not serious	Not serious	Not serious	Not serious	210	210	No significant difference between groups	High

IUD, intrauterine device; RCT, randomized clinical trial; SD, standard deviation

Footnotes

*Effect was statistically significant and clinically relevant.

[a]Effect includes separate results from multiple studies examining the same outcome.

[b]Inconsistency is considered serious due to varying results among studies.

[c]Imprecision is considered serious due to the small number of events.

[d]Risk of bias is considered serious due to the lack of information regarding allocation concealment.

[e]Imprecision is considered serious due to the small sample size.

[f]Inconsistency is considered very serious due to opposing results between studies.

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2.6 Provision of medications for intrauterine device (IUD) placement: Dinoprostone

Systematic review question: Among patients receiving an interval IUD (i.e., placement outside the postabortion or postpartum period), does the use of dinoprostone affect patient or provider outcomes compared with placebo or no treatment? This table is based on Abu-Zaid A, Alshahrani MS, Albezrah NA, Miski NT, Abuzaid M, Aboudi SA, et al. Vaginal dinoprostone versus placebo for pain relief during intrauterine device insertion: a systematic review and meta-analysis of randomised controlled trials. Eur J Contracept Reprod Health Care 2021;26:357-66. 10.1080/13625187.2021.1891411

Methods: All effects presented below are from pooled meta-analysis.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Vaginal dinoprostone vs. placebo										
Patient Pain										
Pain during tenaculum placement	3[1-3]	RCT	Not serious	Not serious	Not serious	Not serious	188	188	SMD (95% CI): -0.79 (-1.43, -0.16)*	High
Pain during uterine sounding	3[1-3]	RCT	Not serious	Not serious	Not serious	Not serious	188	188	SMD (95% CI): -0.88 (-1.54, -0.22)*	High
Pain during IUD placement	5[1-5]	RCT	Not serious	Not serious	Not serious	Not serious	388	388	SMD (95% CI): -1.18 (-1.74, -0.61)*	High
Pain 10-30 minutes after IUD insertion	4[1-4]	RCT	Not serious	Not serious	Not serious	Not serious	288	288	SMD (95% CI): -0.57 (-1.19, 0.05)	High
Provider Ease of Placement										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Ease of insertion	5[1-5]	RCT	Not serious	Not serious	Not serious	Not serious	388	388	SMD (95% CI): -1.17 (-1.62, -0.73)*	High
Need for Adjunctive Placement Measures										
Analgesia	4[1-4]	RCT	Not serious	Not serious	Not serious	Not serious	288	288	RR (95% CI): 0.34 (0.22, 0.53)*	High
Side Effects										
Fever	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 3.73 (1.47, 9.44)*	Low
Nausea	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 1.03 (0.69, 1.53)	Low
Vomiting	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 2.11 (0.97, 4.61)	Low
Diarrhea	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 2.78 (0.95, 8.09)	Low
Shivering	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 2.38 (0.96, 5.90)	Low
Abdominal cramping	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	RR (95% CI): 1.76 (0.73, 4.26)	Low
Post-procedural bleeding	3[1, 4, 5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	280	280	RR (95% CI): 1.02 (0.92, 1.14)	Low
Adverse Events										
Vasovagal reaction	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	None reported	Very Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Uterine perforation	5[1-5]	RCT	Not serious	Not serious	Very serious[a]	Not serious	388	388	None reported	Very Low
Patient Satisfaction with Procedure										
Patient satisfaction	4[1-4]	RCT	Not serious	Not serious	Not serious	Not serious	288	288	SMD (95% CI): 1.41 (0.62, 2.20)*	High

CI, confidence interval; IUD, intrauterine device; RCT, randomized clinical trial; RR, risk ratio; SMD, standard mean difference

Footnotes

*Statistically significant.

[a]Imprecision is considered very serious due to the rarity of events.

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3. Bleeding irregularities (including amenorrhea) with LNG-IUD use

Systematic review question: Among patients experiencing bleeding irregularities while using LNG-IUDs, does the use of a specific treatment compared with no treatment, placebo, or an alternative treatment affect bleeding irregularities? This table is based on van der Heijden P, Tibosch RMG, Geomini P, et al. What is the best drug treatment for premenopausal women with bleeding irregularities using the levonorgestrel-releasing intrauterine system? A systematic review. Eur J Contracept Reprod Health Care. 2020;25:484-91.

Methods: All effects presented below are from individual estimates; no meta-analysis was conducted.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Oral Tranexamic Acid vs. placebo										
Reduction of median number of bleeding/ spotting days	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	63	61	No significant reduction of median number of bleeding/spotting days (Tranexamic acid group: 25 [range of 13-40] vs. placebo group: 33 [15-53.5] [unknown p-value])	High
Adverse events	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	63	61	2 reported	High
Mefenamic Acid vs. placebo										
Reduction of median number of	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	63	61	No significant reduction of median number	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
bleeding/ spotting days									of bleeding/spotting days (Mefanamic acid group: 29 [range of 15-44] vs. placebo group: 33 [15-53.5] [unknown p-value])	
Adverse events	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	63	61	None	High
UPA vs. placebo										
Reduction of bleeding/ spotting days	1[2]	RCT	Serious[c]	Not serious	Not serious	Not serious	15	10	No significant reduction of bleeding/spotting days (UPA group: 13.5 vs. placebo group: 16.5 [p-value= 0.49])	Moderate
Adverse events	1[2]	RCT	Serious[c]	Not serious	Not serious	Not serious	15	10	None	Moderate
Oral Estradiol vs. placebo										
Reduction of bleeding days	1[3]	Non-comparative cohort	Very serious[d,f,g]	Not serious	Serious[d]	Not serious	19	N/A	Significant reduction in number of bleeding days (Before: 68% vs. After: 32%)	Very low
Adverse events	1[3]	Non-comparative cohort	Very serious[d,f,g]	Not serious	Serious[d]	Not serious	19	N/A	None	Very low

IUD, intrauterine device; N/A, non-applicable; UPA, ulipristal acetate

Footnotes

[a]Risk of bias is considered serious due to lack of blinding and placebo control for one arm of the trial.

[b]Risk of bias is considered very serious due to differing group sizes with no explanation.

[c]Risk of bias is considered serious or very serious due to high loss to follow-up.

[d]Imprecision is considered very serious due to small sample size.

[e]Risk of bias is considered very serious due to lack of power calculations.

[f]Risk of bias is considered very serious due to lack of comparison with an age-matched group.

[g]Risk of bias is considered very serious due to uncertain risk of confounding.

References

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4. Bleeding irregularities (including amenorrhea) during implant use

4.1 Evidence summary for additional interventions for which evidence suggested no positive effect or evidence was too limited to make a recommendation

Additional interventions for which evidence suggested no positive effect or evidence was too limited to make a recommendation

Evidence on several other interventions was identified, including aspirin (1 trial), LNG pills (1 trial), mifepristone (3 trials), ulipristal acetate (1 trial), doxycycline alone (2 trials), doxycycline combined with EE (1 trial), doxycycline combined with mifepristone (1 trial), and Vitamin E (2 trials). For these interventions, the evidence either suggested no positive effect on the outcomes assessed or the evidence was too limited to make a recommendation. A detailed summary of the evidence is provided below for each intervention.

Intervention category	**Evidence summary**	**Certainty of evidence**
Aspirin	Use of aspirin (80mg) daily with or without Vitamin E (200mg) daily for 10 days did not result in differences in median length of bleeding and spotting days after treatment initiation or median length of bleed-free interval after treatment compared with placebo in LNG contraceptive implant users.[1] No trials investigated aspirin among ENG implant users.	High
LNG pills	In one trial with a non-random method of allocation (i.e., assigned systematically, in sequence of enrollment) among LNG implant users, LNG pills (30mcg) twice daily for 20 days improved bleeding only after treatment cessation.[2]	Low
Mifepristone	Among LNG implant users, mifepristone (50mg) administered once every 28 days reduced the number of bleeding or spotting days compared with baseline but only after 6 months of treatment; similar bleeding changes were observed in the placebo group.[3] Differences in time to bleeding cessation were not found among ENG implant users taking mifepristone but were found with combining mifepristone with either EE or doxycycline; however, there were no differences in bleed-free intervals or bleeding and spotting days after treatment cessation.[4, 5]	Moderate to High
Ulipristal acetate	Ulipristal acetate (15mg) daily for 7 days decreased time to bleeding episode cessation and decreased bleeding days following treatment cessation compared with placebo among ENG implant users in one trial.[6]	High

Intervention category	Evidence summary	Certainty of evidence
Doxycycline	In one study, doxycycline (500mg) twice daily for 5 days decreased time to bleeding cessation compared with placebo among ENG implant users, but in a second trial, doxycycline alone did not improve time to bleeding cessation.[4, 5] Differences in time to bleeding cessation were not found among ENG implant users taking doxycycline combined with EE but were found when combining doxycycline with mifepristone.[5]There were no differences in bleed-free intervals or bleeding and spotting days after treatment cessation among users of any doxycycline regimen compared with placebo.[4, 5]	Low to Moderate
Vitamin E	In one small study, vitamin E was associated with a reduction in the mean number of bleeding days 30 days after initiating the first treatment cycle among LNG implant users;[7] however, another larger study reported no differences in number of bleeding or spotting days after treatment initiation or in duration of bleed-free interval after treatment with vitamin E (200 mg) daily for 10 days compared with placebo.[8] No trials investigated vitamin E use among ENG implant users	Moderate to High

4.2 Bleeding irregularities (including amenorrhea) during implant use

Systematic review question: Among patients experiencing bleeding irregularities while using contraceptive implants, does the use of a specific treatment compared with no treatment, placebo, or an alternative treatment affect bleeding irregularities? This table is based on Cohen M, Snyder E, Clark E, Nguyen AT, Folger S, Whiteman M, Curtis KM, Gaffield ML. Management of bleeding irregularities during contraceptive implant use: A systematic review. Contraception 2024: in preparation.

Methods: All effects presented below are from individual estimates; no meta-analysis was conducted.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
NSAIDs										
Celecoxib (200mg) vs. placebo - LNG										
Percentage who stopped bleeding within 7 days of initiating treatment	1[9]	RCT	Not serious	Not serious	Not serious	Not serious	20	20	70% of celecoxib group vs. 0% of placebo group (p<0.0001)	High
Bleeding/spotting days in 28 days after initiating treatment	1[9]	RCT	Not serious	Not serious	Not serious	Not serious	20	20	Mean (SD) days: 5.0±1.65 for celecoxib group vs. 19.0±6.50 for placebo group (p<0.001)	High
Duration of bleed-free interval in	1[9]	RCT	Not serious	Not serious	Not serious	Not serious	20	20	Mean (SD) days: 24.0±1.65 for celecoxib group vs.	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
28 days after initiating treatment									10.0±6.50 for placebo group (p<0.001)	
Satisfaction with treatment	1[9]	RCT	Not serious	Not serious	Not serious	Not serious	20	20	80% of celecoxib group vs. 30% of placebo group satisfied (p<0.001)	High
Mefenamic acid (500mg BID) vs. placebo - LNG										
Percentage who stopped bleeding within 7 days of initiating treatment	1[10]	RCT	Not serious	Not serious	Not serious	Not serious	34	33	26/34 (76%) of mefenamic acid group vs. 9/33 (27%) of placebo group (p<0.001)	High
Maintenance of bleeding-free interval 20 days or longer	1[10]	RCT	Not serious	Not serious	Not serious	Not serious	34	33	23/34 (68%) of mefenamic acid group vs. 11/33 (33%) of placebo group (p<0.01)	High
Mean total number bleeding/spotting days within 28 days of treatment initiation	1[10]	RCT	Not serious	Not serious	Not serious	Not serious	34	33	Mean±SD days: 11.6±8.2 for mefenamic acid group vs. 17.2±10.2 for placebo group (p<0.05)	High
Mefenamic acid (500mg TID) vs. placebo - ENG										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Proportion who stopped bleeding within 7 days of treatment initiation	1[11]	RCT	Not serious	Not serious	Not serious	Not serious	23	23	15/23 (65.2%) of mefenamic acid group vs. 5/23 (21.7%) of placebo group (p<0.05)	High
Proportion who stopped bleeding for > 20 days within 28 days of treatment initiation	1[11]	RCT	Not serious	Not serious	Not serious	Not serious	23	23	13/23 (56.5%) of mefenamic acid group vs. 5/23 (21.7%) of placebo group (p<0.05)	High
Total number of bleeding/spotting days over 28 days	1[11]	RCT	Not serious	Not serious	Not serious	Not serious	23	23	Mean bleeding/spotting days: 10.52 for mefenamic acid group vs. 16.78 for placebo group (p<0.05)	High
Mefenamic acid (500mg TID) vs. COC (150 mcg desogestrel + 20 µg EE)- ENG										
Percent who stopped bleeding within 7 days of treatment	1[12]	RCT	Very serious[a, b]	Not serious	Not serious	Not serious	42	42	32/42 (76%) of COC group vs. 15/42 (35.7%) of mefenamic acid group (p<0.05)	Very Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Recurrence of bleeding after stopping treatment for ≥7 days	1[12]	RCT	Very serious[a, b]	Not serious	Not serious	Not serious	42	42	6 (14.3%) of COC group vs. 3 (7.1%) of mefenamic acid group (p=0.919)	Very Low
Duration of bleeding within 90 days of treatment	1[12]	RCT	Very serious[a, b]	Not serious	Not serious	Not serious	42	42	Mean±SD days: 7.29±3.16 for COC group vs. 10.57±4.14 for mefenamic acid group (p<0.05)	Very Low
Ibuprofen (800mg TID) vs. placebo - LNG										
Mean number of bleeding/spotting days in 5 days after initiating treatment	1[13]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	42	44	Mean days: 0.75 for ibuprofen group vs. 1.16 for placebo group (p-value NS)	Low
Mean number of bleeding/spotting days in 10 days after initiating treatment	1[13]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	42	44	Mean days: 1.76 for ibuprofen group vs. 2.17 for placebo group (p-value NS)	Low
Bleeding/spotting days in 30 days after	1[13]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	42	44	Mean (SD) days: 6.2 (2.55) for ibuprofen group vs. 6.4 (2.30) for	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
initiating treatment									placebo group (p-value NS)	
Bleeding/spotting days in days 1-5 after initiating treatment	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	21	21	Mean days: 2.9 for ibuprofen group vs. 3.6 for placebo group (p-value NS)	Very Low
Bleeding/spotting days in days 1-20 after initiating treatment	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	21	21	Mean days: 5.9 for ibuprofen group vs. 11.1 for placebo group (significant, p-value NR)	Very Low
Total bleeding/spotting days over 365-day follow-up (multiple courses allowed)	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	21	21	Mean days: 94 for ibuprofen group vs. 129 for placebo group (significant, p-value NR)	Very Low
Aspirin (80mg) vs. placebo - LNG										
Consecutive bleeding/spotting days after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	117	116	Median days: 6 for aspirin group, 7 for Vitamin E group, 7 for vitamin E + aspirin group, 7 for placebo group (p=0.19)	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Duration of bleed-free interval after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	115	111	Median days: 15 for aspirin group, 16 for vitamin E group, 16 for vitamin E + aspirin group, 15 for placebo group (p=0.96)	High
Aspirin (80mg) + Vitamin E (200mg) vs. placebo - LNG										
Consecutive bleeding/spotting days after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	114	116	Median days: 7 for Vit E+aspirin group, 6 for aspirin group, 7 for Vitamin E group, 7 for placebo group (p=0.19)	High
Duration of bleed-free interval after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	112	111	Median days: 16 for Vit E+aspirin group, 15 for aspirin group, 16 for vitamin E group, 15 for placebo group (p=0.96)	High
Anti-fibrinolytic Agents										
Tranexamic acid (500mg BID) vs. placebo - LNG										
Percentage who stopped bleeding within 7 days of	1[14]	RCT	Not serious	Not serious	Not serious	Not serious	34	34	64.7% of tranexamic acid group vs. 35.3% of placebo group (p=0.015)	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
initiating treatment										
Percentage who had a bleeding-free interval >20 days	1[14]	RCT	Not serious	Not serious	Not serious	Not serious	34	34	58.8% of tranexamic acid group vs. 76.5% of placebo group (p=0.12)	High
Duration of bleeding days after treatment	1[14]	RCT	Not serious	Not serious	Not serious	Not serious	34	34	Mean days: 15.4 for tranexamic acid group vs. 12.7 for placebo group (p=0.182)	High
Hormonal Treatment										
COC (150 mg LNG + 30 µg EE) vs. placebo - ENG										
Proportion who stopped bleeding within 14 day treatment course	1[15]	RCT	Not serious	Not serious	Not serious	Not serious	16	16	14/16 (87.5%) in COC group vs. 6/16 (37.5%) in placebo group (p<0.01)	High
Proportion who stopped bleeding within 28 day treatment course	1[16]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	12	12	12/12 in COC group vs. 8/12 (75%) in placebo group (p=0.09)	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Days to stop bleeding after initiating treatment	2[15, 16]	RCT	Serious[c, f]	Not serious	Serious[d]	Not serious	26	14	Median (range) days: 5.0 (1-13) in COC group vs. 9.0 (5-14) in placebo group (p=0.05) (Guiahi); 1 (1-9) in COC group vs. 4.5 (1-28) in placebo group (p=0.63) (Hou)	Low
Days without bleeding during treatment	1[15]	RCT	Not serious	Not serious	Not serious	Not serious	16	16	Median (range) days: 9.0 (1-13) in COC group vs. 3.5 (0-11) in placebo group (p=0.03)	High
Days to restart bleeding/spotting after treatment	1[15]	RCT	Serious[f]	Not serious	Not serious	Not serious	14	6	Median (range) days: 5.5 (1-131) in COC group vs. 10.0 (3-87) in placebo group (p=0.14)	Moderate
Patient-reported bleeding improvement with 4 weeks of treatment	1[16]	RCT	Serious[c]	Not serious	Serious[d]	Not serious	12	12	"Significant improvement": 11/12 (92%) in COC group vs. 5/12 (42%) in placebo group (p=0.03)	Low
COC (150 mcg LNG + 30mcg EE) vs. placebo - LNG										
Episodes of bleeding/spotting	1[17]	RCT	Very serious[g, h]	Not serious	Not serious	Serious[i]	16	14	COC: 3.4+0.3 90 days pre-treatment vs. 3.3+0.2 90 days post-treatment (NS); Placebo:	Very Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									3.4+0.4 90 days pre-treatment vs. 3.5+0.5 90 days post-treatment (NS); no direct comparison	
Total bleeding/spotting days	1[17]	RCT	Very serious[g,h]	Not serious	Not serious	Serious[i]	16	14	Total days: COC: 35.8±4.1 90 days pre-treatment vs. 18.2±1.9 90 days post-treatment (p<0.05); Placebo: 34.7±3.5 90 days pre-treatment vs. 28.6±5.4 90 days post-treatment (NS); no direct comparison	Very Low
Number of bleeding/spotting days per episode	1[17]	RCT	Very serious[g,h]	Not serious	Not serious	Serious[i]	16	14	Total days: COC: 11.9±1.5 90 days pre-treatment vs. 5.8+0.6 90 days post-treatment (p<0.05); Placebo: 13.2±2.6 90 days pre-treatment vs 12.4±5.8 90 days post-treatment (NS); no direct comparison	Very Low
Reduction in number of bleeding/sp	1[17]	RCT	Very serious[g,h]	Not serious	Not serious	Serious[i]	18	14	COC group not significantly decreased; Placebo not significantly	Very Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
otting days during treatment									decreased (values NR, no direct comparison)	
COC (250 mcg LNG + 50mcg EE) vs. placebo - LNG										
Percentage who stopped bleeding within 3 days of initiating treatment	1[18]	RCT	Serious[a,j]	Not serious	Not serious	Not serious	45	46	91% of COC group vs. 15% of placebo group (p<0.0005)	Moderate
Bleeding/s potting days in 20 days after initiating treatment	1[18]	RCT	Serious[a,j]	Not serious	Not serious	Serious[i]	45	46	Mean (SD) days: 2.6 (1.4) for COC group vs. 12.3 (5.4) for placebo group (p<0.00001)	Low
Percentage with bleeding-free interval ≥20 days after initiating treatment	1[18]	RCT	Serious[a,j]	Not serious	Not serious	Not serious	45	42	40/45 (89%) of COC group vs. 11/42 (26%) of placebo group (p<0.0005)	Moderate
COC (150 mcg desogestrel + 20 µg EE) vs. mefenamic acid (500mg TID)- ENG										
Percent who stopped bleeding within 7	1[12]	RCT	Very serious[a,b]	Not serious	Not serious	Not serious	42	42	32/42 (76%) of COC group vs. 15/42 (35.7%) of mefenamic acid group (p<0.05)	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
days of treatment										
Recurrence of bleeding after stopping treatment for ≥7 days	1[12]	RCT	Very serious[a, b]	Not serious	Not serious	Not serious	42	42	6 (14.3%) of COC group vs. 3 (7.1%) of mefenamic acid group (p=0.919)	Low
Duration of bleeding within 90 days of treatment	1[12]	RCT	Very serious[a, b]	Not serious	Not serious	Not serious	42	42	Mean±SD days: 7.29±3.16 for COC group vs. 10.57±4.14 for mefenamic acid group (p<0.05)	Low
EE (50 mcg) vs. placebo - LNG										
Percentage who stopped bleeding within 3 days of initiating treatment	1[18]	RCT	Serious[a ,j,n]	Not serious	Not serious	Not serious	43	46	67% of EE group vs. 15% of placebo group (p<0.0005)	Moderate
Bleeding/s potting days over 20 days of treatment	1[18]	RCT	Serious[a ,j,n]	Not serious	Not serious	Not serious	43	46	Mean (SD) days: 5.4 (5.1) days for EE group vs. 12.3 (5.4) days for placebo group (p<0.00001)	Moderate
Percentage with bleeding-free	1[18]	RCT	Serious[a ,j,n]	Not serious	Not serious	Not serious	42	42	27 (64%) of EE group vs. 11 (26%) of placebo group (p<0.005)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
interval ≥20 days after initiating treatment										
Total Bleeding/spotting days	1[17]	RCT	Very serious[g, h]	Not serious	Not serious	Serious[i]	18	14	Total days: EE: 38.0±2.7 90 days pre-treatment vs. 19.2±3.4 90 days post-treatment (p<0.05); Placebo: 34.7±3.5 90 days pre-treatment vs. 28.6±5.4 90 days post-treatment (NS), no direct comparison	Very Low
Number of bleeding/spotting days per episode	1[17]	RCT	Very serious[g, h]	Not serious	Not serious	Serious[i]	18	14	Total days: EE: 14.7±2.9 90 days pre-treatment vs. 6.7±1.6 90 days post-treatment (p<0.05); Placebo: 13.2±2.6 90 days pre-treatment vs 12.4±5.8 90 days post-treatment (NS), no direct comparison	Very Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Episodes of bleeding/spotting	1[17]	RCT	Very serious[g, h]	Not serious	Not serious	Serious[i]	18	14	EE: 3.4+0.4 90 days pre-treatment vs. 3.0+0.2 90 days post-treatment (NS); Placebo: 3.4+0.4 90 days pre-treatment vs. 3.5+0.5 90 days post-treatment (NS); no direct comparison	Very Low
Reduction in number of bleeding/spotting days during treatment	1[17]	RCT	Very serious[g, h]	Not serious	Not serious	Serious[i]	18	14	EE significantly decreased (p<0.02, no values reported); Placebo not significantly decreased (no values reported); no direct comparison	Very Low
Bleeding/spotting days in 20 days after initiating treatment	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	17	21	4.5 for EE group vs. 11.1 for placebo group (significant, p-value NR)	Low
Total bleeding/spotting days over 365-day follow-up (multiple	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	17	21	77 for EE group vs. 129 for placebo group (significant, p-value NR)	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
courses allowed)										
EE (20mcg) vs. placebo - LNG										
Mean number of bleeding/spotting days in 10 days after initiating treatment	1[13]	RCT	Very serious[c, k]	Not serious	Serious[d]	Not serious	20	44	Mean days: 2.35 for EE group vs. 2.17 for place group (p-value NS)	Very Low
Bleeding/spotting days in 30 days after initiating treatment	1[13]	RCT	Very serious[c, k]	Not serious	Serious[d]	Not serious	20	44	Mean (SD) days: 6.1 (2.63) for EE group vs. 6.4 (2.30) for placebo group (p-value NS)	Very Low
Estradiol (100mcg) patch vs. placebo - LNG										
Proportion who showed clinical improvement (bleeding <8 days and/or interval >20 days)	1[19]	RCT	Serious[j]	Not serious	Very serious[l]	Not serious	33	31	23/33 in estraderm patch group vs. 13/31 in placebo group (p-value NR)	Very Low
LNG (30 mcg BID) vs. placebo - LNG										
Bleeding/spotting	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	21	21	8.9 for LNG group vs. 11.1 for	Low

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
days in 20 days after initiating treatment									placebo group of days 1-20 after initiating treatment (p-value NS)	
Total bleeding/spotting days over 365-day follow-up	1[2]	NRT	Serious[e]	Not serious	Not serious	Not serious	21	21	101 for LNG group vs. 129 for placebo group (significant, p-value NR)	Low
Mifepristone (25mg BID) + EE (20 mcg) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	2[4, 5]	RCT	Not serious	Not serious	Not serious	Not serious	82	81	Mean days (95% CI) days: 4.2 days (3.5-5.2) for Mife + EE vs 7.5 days (6.1-9.1) for placebo (p<0.05) (Weisberg 2006); Mife+EE: 4.0 days (3.5-4.6) vs Placebo: 6.4 days (5.1-8.0) (p<0.001) (Weisberg 2009)	High
Duration of bleed-free interval after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	82	81	Mean (95% CI) days: 11.2 (9.0-13.9) for mife + EE vs. 15.3 (12.4-19.1) for placebo (p-value NS) (Weisberg 2006); No significant differences (values	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									NR) (Weisberg 2009)	
Episodes of bleeding/spotting after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	82	81	Mean (95% CI): 4.0 (3.5-4.5) for mife +EE vs. 4.1 (3.6-4.7) for placebo (p-value NS) (Weisberg 2006); No significant differences (values NR) (Weisberg 2009)	Moderate
Doxycycline (100mg BID) + EE (20mcg) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	Mean (95% CI) days: 6.4 (4.8-8.6) for doxycycline+EE group vs. 6.4 (5.1-8.0) for placebo group (p=NS)	Moderate
Duration of bleed-free interval after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate
Episodes of bleeding/spotting after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
SERM/SPRM										
SERM: Tamoxifen (10 mg BID) vs. placebo - LNG										
Percentage who stopped bleeding within 7 days of initiating treatment	1[20]	RCT	Not serious	Not serious	Not serious	Not serious	50	50	41 (82%) of tamoxifen group vs. 28 (56%) of placebo group (p=0.005)	High
Bleeding/spotting days after initiating treatment	1[20]	RCT	Not serious	Not serious	Not serious	Not serious	50	50	Mean±SD days: 1st month: 6.24±0.70 for Tamoxifen group vs. 12.29±0.84 for placebo group (p=0.0003); 2nd month: 6.78±0.91 vs. 11.87±0.83 (p=0.0008)	High
Duration of bleed-free interval after treatment	1[20]	RCT	Not serious	Not serious	Not serious	Not serious	50	50	Mean±SD days: 33.2±20.9 days for Tamoxifen group vs. 15.7±12.9 days for placebo group (p=0.0003)	High
Satisfaction with treatment	1[20]	RCT	Not serious	Not serious	Not serious	Not serious	50	50	After 1st month: 85.7% for tamoxifen group vs. 34.7% for placebo group (p<0.0005); After 2nd month: 75.5%	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									for tamoxifen group vs. 23.9% for placebo group (p<0.0005)	
SERM: Tamoxifen (10mg BID) vs. placebo - ENG										
Bleeding/spotting days in 30 days after initiating treatment	1[21]	RCT	Not serious	Not serious	Not serious	Not serious	26	25	Mean±SD days: 10.5±9.0 for tamoxifen group vs. 15.5±8.5 for placebo group (p=0.05)	High
Total days amenorrhea in 1st 90 days	1[22]	RCT	Not serious	Not serious	Not serious	Not serious	46	42	Median (range): 60 (18-84) for tamoxifen group vs. 52 (11-67) for placebo group (p=0.002)	High
Days to stop bleeding after initiating treatment	2[21, 22]	RCT	Not serious	Not serious	Not serious	Not serious	79	76	Median days: 5 for tamoxifen group vs. 6 for placebo group (NS); Median (range) days: 5 (1-21) for tamoxifen group vs. 6 (1-26) for placebo group (p=0.029)	High
Consecutive amenorrhea days after first treatment	2[21, 22]	RCT	Not serious	Not serious	Not serious	Not serious	80	76	Mean±SD days: 28.8±24.5 for tamoxifen group vs. 13.6±19.2 for placebo group, mean difference	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
									15.2 (95% CI: 2.8, 27.5) (p=0.02) (Simmons); Tamoxifen vs. placebo: 9.8 more days (95% CI 4.6-15.0) (Edelman)	
Satisfaction with bleeding pattern after 1st treatment	2[21, 22]	RCT	Not serious	Not serious	Not serious	Not serious	76	73	Mean satisfaction VAS score: 70.3 mm for tamoxifen group vs. 49.3 mm for placebo group (p= 0.02); Median (range) satisfaction VAS score: 71 (8.5-100) for tamoxifen group vs. 31 (0-100) for placebo group (p<0.001)	High
Satisfaction with bleeding pattern after 90 days	1[22]	RCT	Not serious	Not serious	Not serious	Not serious	45	44	Median (range) satisfaction VAS score: 62 (16-100) tamoxifen vs. 46 (0-100) placebo (p=0.023)	High
Satisfaction with bleeding pattern after 180 days	1[21]	RCT	Serious[c]	Not serious	Not serious	Not serious	22	21	Mean±SD satisfaction VAS score: 61.4±24.7 for tamoxifen group vs. 53.6±33.3 for placebo group (p=0.39)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
SPRM: Mifepristone (50mg) vs. placebo - LNG										
Bleeding/spotting days in 90 day reference period after initiating treatment (includes 4 monthly treatments)	1[3]	RCT	Not serious	Not serious	Not serious	Serious[i]	50	50	Mean days: Mife: 48±15 in 1st 90d reference period (no treatment) vs. 29 in 2nd 90d reference period (p<0.0002); Placebo: 51±15 in 1st 90d reference period (no treatment) vs. 33 in 2nd 90d reference period (p<0.0002), no direct comparison	Moderate
Duration of bleeding episodes after initiating treatment	1[3]	RCT	Not serious	Not serious	Not serious	Serious[i]	50	50	Mife: 14 days in 1st 90d reference period (no treatment) vs 6.5 days in 2nd 90d reference period (p<0.0001); Placebo: 15 in 1st 90d reference period (no treatment) vs. 11.1 days n 2nd 90d reference period (p=0.0003); no direct comparison	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Satisfaction with treatment	1[3]	RCT	Not serious	Not serious	Not serious	Serious[i]	48	49	37% for mifepristone group vs. 18% for placebo group (p<0.01)	Moderate
SPRM: Mifepristone (25mg BID) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	1[4]	RCT	Not serious	Not serious	Not serious	Not serious	42	44	Mean (95% CI) days: 5.9 (4.8-7.2) for mifepristone group vs. 7.5 (6.1-9.1) for placebo group (p=0.283)	High
Duration of bleed-free interval after initiating treatment	1[4]	RCT	Not serious	Not serious	Not serious	Not serious	42	44	Mean (95% CI) days: 10.4 (8.3-13.0) for mifepristone vs. 15.3 (12.4-19.1) for placebo (p-value NS)	High
Episodes of bleeding/spotting after initiating treatment	1[4]	RCT	Not serious	Not serious	Not serious	Not serious	42	44	Mean (95% CI) days: 4.7 (4.1-5.3) for mifepristone group vs. 4.1 (3.6-4.7) for placebo group (p-value NS)	High
SPRM: Mifepristone (25mg BID) + EE (20 mcg) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until	2[4, 5]	RCT	Not serious	Not serious	Not serious	Not serious	82	81	Mean days (95% CI) days: 4.2 days (3.5-5.2) for Mife + EE vs 7.5 days (6.1-9.1) for placebo (p<0.05); Mife+EE:	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
bleeding stopped									4.0 days (3.5-4.6) vs placebo: 6.4 days (5.1-8.0) (p<0.001)	
Duration of bleed-free interval after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	82	81	Mean (95% CI) days: 11.2 (9.0-13.9) for mife + EE vs. 15.3 (12.4-19.1) for placebo (p-value NS) (Weisberg 2006)	Moderate
Episodes of bleeding/spotting after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	82	81	Mean (95% CI): 4.0 (3.5-4.5) for mife +EE vs. 4.1 (3.6-4.7) for placebo (p-value NS) (Weisberg 2006); No significant difference	Moderate
SPRM: Mifepristone (25mg) + Doxycycline (100mg BID) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	Mean (95% CI) days: 4.4 (3.8-5.2) for doxycycline+mifepristone group vs. 6.4 (5.1-8.0) for placebo group (p=0.0108)	Moderate
Duration of bleed-free interval after	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
initiating treatment										
Episodes of bleeding/spotting after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate
SPRM: UPA (15 mg) vs. placebo - ENG										
Bleeding days in 30 days after initiating treatment	1[6]	RCT	Not serious	Not serious	Not serious	Not serious	32	31	Median (IQR) days: 7.0 (4.5-11) for UPA group vs. 12.0 (6-21) for placebo group (p=0.002)	High
Proportion who stopped bleeding by day 10	1[6]	RCT	Not serious	Not serious	Not serious	Not serious	32	31	11/32 (34.4%) of UPA group vs. 3/31 (9.7%) of placebo group (p=0.03)	High
Satisfaction with bleeding pattern after treatment	1[6]	RCT	Not serious	Not serious	Not serious	Not serious	32	31	"Very Happy" 71.9% of UPA group vs. 26.7% of placebo group (p<0.001)	High
Desire to keep implants	1[6]	RCT	Not serious	Not serious	Not serious	Not serious	32	31	89.7% of UPA group vs. 63.3% of placebo group (p=0.03)	High
Doxycycline										
Doxycycline (100 mg BID) vs. placebo -ENG										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Bleeding/spotting days after initiating treatment until bleeding stopped	2[4, 5]	RCT	Not serious	Serious[m]	Serious[d]	Not serious	75	81	Mean (95% CI) days: 4.8 (3.9-5.8) for doxy vs. 7.5 (6.1-9.1) for placebo (p<0.05) (Weisberg 2006); 6.4 (4.4-9.2) for doxy vs. 6.4 (5.1-8.0) for placebo, no significant differences (values NR) (Weisberg 2009)	Low
Duration of bleed-free interval after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	75	81	Mean (95% CI) days: 12.4 (9.9-15.4) for doxy vs. 15.3 (12.4-19.1) for placebo (p-value NS) (Weisberg 2006); No significant differences (values NR) (Weisberg 2009)	Moderate
Episodes of bleeding/spotting after initiating treatment	2[4, 5]	RCT	Not serious	Not serious	Serious[d]	Not serious	75	81	Mean (95% CI): 4.6 (4.0-5.2) for doxy vs. 4.1 (3.6-4.7) for placebo (p-value NS) (Weisberg 2006); No significant differences (values NR) (Weisberg 2009)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Doxycycline (100mg BID) + EE (20mcg) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	Mean (95% CI) days: 6.4 (4.8-8.6) for doxycycline+EE group vs. 6.4 (5.1-8.0) for placebo group (p=NS)	Moderate
Duration of bleed-free interval after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate
Episodes of bleeding/spotting after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate
Mifepristone (25mg) + Doxycycline (100mg BID) vs. placebo - ENG										
Bleeding/spotting days after initiating treatment until bleeding stopped	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	Mean (95% CI) days: 4.4 (3.8-5.2) for doxycycline+mifepristone group vs. 6.4 (5.1-8.0) for placebo group (p=0.0108)	Moderate
Duration of bleed-free interval after	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
initiating treatment										
Episodes of bleeding/spotting after initiating treatment	1[5]	RCT	Not serious	Not serious	Serious[d]	Not serious	35	37	No significant difference (values NR)	Moderate
Vitamin E										
Vitamin E (200mg) vs. placebo - LNG										
Consecutive bleeding/spotting days after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	117	116	Median days: 7 for Vit E group, 7 for Vit E+aspirin group, 6 for aspirin group, 7 for placebo group (p=0.19)	High
Total bleeding/spotting days in 30 days after initiating treatment	1[7]	RCT	Serious[j]	Not serious	Not serious	Not serious	38	34	7.7±1.4 for Vit E group vs. 12.1±1.3 for placebo group (significant, p-value NR)	Moderate
Duration of bleed-free interval after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	112	111	Median days: 16 for Vit E group, 16 for Vit E+aspirin group, 15 for aspirin group, 15 for placebo group (p=0.96)	High
Vitamin E (200mg) + Aspirin (80mg) vs. placebo - LNG										

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Consecutive bleeding/spotting days after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	114	116	Median days: 7 for Vit E+aspirin group, 6 for aspirin group, 7 for Vitamin E group, 7 for placebo group (p=0.19)	High
Duration of bleed-free interval after initiating treatment	1[1]	RCT	Not serious	Not serious	Not serious	Not serious	112	111	Median days: 16 for Vit E+aspirin group, 15 for aspirin group, 16 for vitamin E group, 15 for placebo group (p=0.96)	High

BID, twice daily; COC, combined oral contraceptive; EE, ethinyl estradiol; LNG, levonorgestrel; NRT, non-randomized trial; NS, not significant; TID, three times daily; UPA, ulipristal acetate; VAS, visual analog score

Footnotes

[a]Risk of bias is considered serious due to the difference in baseline characteristics between groups, which was not adjusted for in analyses.

[b]Risk of bias is considered serious due to the lack of blinding of study participants or staff.

[c]Risk of bias is considered serious or very serious due to the high loss to follow-up.

[d]Imprecision is considered serious due to the insufficient sample size to meet power calculations.

[e]Risk of bias is considered serious due to the lack of information on participation or compliance.

[f]Risk of bias is considered serious due to participants only being followed if they were not bleeding at the end of the 14-day treatment period.

[g]Risk of bias is considered very serious due to the lack of explanation of the measurement of outcomes.

[h]Risk of bias is considered very serious due to the lack of information on the drop-out rate.

[i]Indirectness is considered serious due to the lack of direct comparison between study groups.

[j]Risk of bias is considered serious due to the lack of explanation of randomization and allocation processes.

[k]Risk of bias is considered serious due to the differential compliance between groups with the study drug.

[l]Imprecision is considered very serious due to the lack of power calculations and statistically significant findings.

[m]Inconsistency is considered serious due to inconsistent results between two studies.

[n]Risk of bias is considered serious due to the treatment and placebo bills not being identical.

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5. Use of regular contraception after emergency contraception pills (ECPs)

Systematic review question: Among women of reproductive age, does initiation or resumption of hormonal contraception immediately or soon after ulipristal acetate (UPA) use influence effectiveness of UPA or effectiveness of hormonal contraception in preventing pregnancy?

This table is based on: Snyder E, Curtis KM, Nguyen AT, Tadikonda A, Kortsmit K, Zapata L, Whiteman MK. Hormonal contraception after the use of ulipristal acetate as emergency contraception: A systematic review. Contraception 2024: in preparation.

Methods: All effects presented below are from individual estimates; no meta-analysis was conducted.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Initiation										
Effect of UPA on the effectiveness of hormonal contraception to suppress ovulation										
Effectiveness (Ovulation)	2[1, 2]	RCT	Not serious	Not serious	Not serious	Serious[a]	68	66	No significant difference (p>0.05)	Moderate
Adverse events	1[1]	RCT	Not serious	Not serious	Serious[b]	Not serious	39	37	None reported	Moderate
Vaginal bleeding	1[1]	RCT	Not serious	Not serious	Serious[b]	Not serious	39	37	No difference	Moderate
Effect of hormonal contraception on the effectiveness of UPA to delay ovulation										
Effectiveness (Ovulation)	1[2]	RCT	Not serious	Not serious	Not serious	Serious[a]	29	29	Increased risk of ovulation with UPA+DSG vs UPA+PLB (p=0.0244)	Moderate

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Effectiveness (Ovulation)	1[3]	Cohort	Not serious	Not serious	Not serious	Serious[a]	33	33	Increased risk of ovulation with UPA+COCs vs UPA alone (p=0.008)	Very Low
Adverse events	1[3]	Cohort	Not serious	Not serious	Serious[b]	Not serious	33	33	None reported	Very Low
Missed pills										
Effect of hormonal contraception on the effectiveness of UPA to delay ovulation										
Effectiveness (Ovulation [days 0-5])	1[4]	RCT	Not serious	Not serious	Not serious	Serious[a]	50	50	No ovulations in either group	Moderate
Effect of UPA on the effectiveness of hormonal contraception to suppress ovulation										
Effectiveness (Ovulation [days 0-26])	1[4]	RCT	Not serious	Not serious	Not serious	Serious[a]	50	50	Increased risk of ovulation with delayed COC start vs immediate COC start after UPA (p= 0.042)	Moderate

COC, combined oral contraceptive; DSG, desogestrel; RCT, randomized clinical trial; UPA, ulipristal acetate

Footnotes

[a]Indirectness is considered serious due to the use of ovulation as a proxy measure for the effectiveness of contraception to prevent pregnancy.

[b]Imprecision is considered serious due to insufficient power to identify outcome.

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