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

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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	Certaint y
Testosterone	users									
Ovulation (PdG > 5 μg/mL for 3 consecutive		Non- comparative	Very		Very				1/22 (5%) ovulated; 1/6 (17%) of new users and 0/16 (0%) of continuing	
Ovulation (PdG > 3 µg/mL for 2	11	cohort Non-	serious ^a	Not serious	serious ^b	Serious ^c	22	N/A	users 8/22 (36%) ovulated; 6/6 (100%) of new users and 2/16 (13%) of	Very low
consecutive days)	1 ¹	comparative cohort	Very serious ^a	Not serious	Very serious ^b	Serious ^c	22	N/A	continuing users	Very low

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

Footnotes

^aRisk of bias is considered very serious due to the low response and follow-up rates.

^bImprecision is considered very serious due to the small sample size.

^cIndirectness is considered serious due to the use of ovulation as a proxy measure for pregnancy risk.

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1. Taub RL, Ellis SA, Neal-Perry G, Magaret AS, Prager SW, Micks EA. The effect of testosterone on ovulatory function in transmasculine individuals. Am J Obstet Gynecol 2020;223:229.e1-.e8. https://doi.org/10.1016/j.ajog.2020.01.059

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).		
<u>NSAIDs</u>	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. 	Low for patient pain and 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. 	
<u>Tramadol</u>	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. 	Low for provider ease of placement, placement success, side effects, adverse events, and patient satisfaction with the procedure; very low for patient pain.
		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.	

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.	Low for patient pain and 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. 	
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).		
<u>Topical</u>	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.	side effects, and adverse events.
		Evidence suggests that topical smooth muscle relaxants do not reduce adverse events, side effects, or need for adjunctive placement measures, nor improve placement success.	
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 v	s. placebo/c	ontrol								
Patient Pain										
Pain during tenaculum placement (10 cm VAS [mean]) Pain during IUD placement (10 cm VAS	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) Mean difference (95% CI): -0.43 (-	High
[mean])	7 ¹⁻⁷	RCT	serious	Serious ^a	Serious ^b	Not serious	386	380	1.30, 0.44) (p=0.33)	Low
Moderate or severe pain during IUD placement									Risk ratio (95% CI): 0.82 (0.58, 1.16)	
(%)	3 ⁸⁻¹⁰	RCT	Serious ^c	Serious ^a	Serious ^b	Not serious	329	339	(p=0.26)	Very low

							Number			
	Number	Chudu	Risk of				of	Number of		
Outcome	of studies	Study design	Bias	Inconsistency	Imprecision	Indirectness	patients: treatment	patients: comparison	Effect	Certainty
Highest level				,				ССТРОПОСТ		
of pain after										
IUD										
placement										
and before										
clinic									Mean difference	
discharge (10 cm VAS			Not						(95% CI): 0.08 (-	
[mean])	5 ^{1-3, 7, 11}	RCT	serious	Serious ^a	Not serious	Not serious	226	222	0.59, 0.74) (p=0.82)	Moderate
[iiieaii])	J , ,	KCI	serious	Serious	Not serious	Not serious	220	222	Median (range): 7.0	Moderate
									(2.5-10) for	
Pain during									misoprostol group	
IUD									vs. 6.5 (0-10) for	
placement									control group	
(10 cm VAS									(p=0.20); median	
[median])	112	RCT	Serious ^d	Not serious	Serious ^{e,f}	Not serious	39	40	difference: 0.5	Low
									Median (range): 4.6	
									(1.1-9.2) for	
Pain during									misoprostol group	
IUD									vs. 3.4 (0-9.0) for	
placement (10 cm VAS			Not						control group (p=0.044); median	
[median])	1 ¹³	RCT	serious	Not serious	Serious ^{e,f}	Not serious	37	36	difference: 1.2	Moderate
Highest level		INCI	3011003	1401 3011003	3011003	1400 3011003	37	30	difference. 1.2	Wioderate
of pain after										
IUD									Median (range): 3.6	
placement									(0.1-10.0) for	
and before									misoprostol group	
clinic									vs. 2.1 (0-8.6) for	
discharge									control group	
(10 cm VAS			Not						(p=0.024); median	
[median])	1 ¹³	RCT	serious	Not serious	Serious ^{e,f}	Not serious	37	36	difference: 1.5*	Moderate
Provider Ease	of Placeme	nt								

							Number			
	Number						of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Easy									Risk ratio (95% CI):	
placement			Not						1.30 (0.85, 1.98)	
(%)	38, 10, 12	RCT	serious	Serious ^a	Serious ^b	Not serious	168	179	(p=0.24)	Moderate
Provider										
ease of										
placement									Mean difference	
(10 cm VAS			Not						(95% CI): -0.85 (-	
[mean])	8 ^{1-7, 11}	RCT	serious	Serious ^a	Serious ^b	Not serious	428	420	1.65, -0.05) (p=0.04)	Low
									Median (range): 2.1	
									(0-10) for	
Provider									misoprostol group	
ease of									vs. 2.1 (0-6.8) for	
placement									control group	
(10 cm VAS			Not						(p=0.75); median	
[median])	1 ¹³	RCT	serious	Not serious	Serious ^{e,f}	Not serious	37	36	difference: 0.0	Moderate
Need for Adju	inctive Place	ment Me	asures	1	l	l				
Ultrasound									Risk ratio (95% CI):	
guidance			Not						0.71 (0.09, 5.86)	
(%)	3 ^{6, 7, 13}	RCT	serious	Not serious	Serious ^{b,f}	Not serious	121	118	(p=0.75)	Moderate
Local									Risk ratio (95% CI):	
anesthesia	2.50.40		Not						1.31 (0.85, 2.04)	
(%)	5 ^{2, 6-8, 13}	RCT	serious	Not serious	Serious ^{b,f}	Not serious	181	182	(p=0.22)	Moderate
									Peto odds ratio	
_									(95% CI): not	
Analgesia	. 0		Not						estimable due to 0	
(%)	18	RCT	serious	Not serious	Serious ^f	Not serious	43	46	events observed	Moderate
Cervical										
dilation (for										
patients										
with recent										
failed									Risk ratio (95% CI):	
placement	4 1/1	207	Not		a hf			40	0.88 (0.56, 1.36)	
attempt) (%)	114	RCT	serious	Not serious	Serious ^{b,f}	Not serious	48	42	(p=0.55)	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Cervical										
dilation (for										
patients										
without									D: 1 .: (050/ CI)	
recent failed			NI-+						Risk ratio (95% CI):	
placement	6 ^{2, 5-8, 13}	DOT	Not		6 · h		202	270	0.84 (0.38, 1.85)	
attempt) (%)		RCT	serious	Not serious	Serious ^b	Not serious	283	279	(p=0.66)	Moderate
Placement Su	ccess	Τ	I	T	I	T			T	
Placement										
success (for										
patients										
without										
recent prior									D: 1 .: (050/ CI)	
failed			NI-+						Risk ratio (95% CI):	
placement	12 ^{1-7, 9-13}	RCT	Not	Comingue	Natassia	Not comicate	790	789	1.01 (0.98, 1.04)	NA a da wata
attempt) (%) Placement	12- 1,1	RCI	serious	Serious ^a	Not serious	Not serious	790	789	(p=0.42)	Moderate
success (for										
patients										
with recent										
prior failed									Risk ratio (95% CI):	
placement			Not						1.41 (1.09, 1.83)	
attempt) (%)	114	RCT	serious	Not serious	Serious ^{b,f}	Not serious	48	42	(p=0.009)*	Moderate
Side Effects		1.01	3011003	1100 3011003	3011043	11013011003		,,_	(p 0.003)	Moderate
Side Lifects									Risk ratio (95% CI):	
	81, 2, 5, 6, 8,		Not						1.42 (0.80, 2.55)	
Nausea (%)	10-12	RCT	serious	Not serious	Serious ^b	Not serious	399	404	(p=0.24)	Moderate
.100500 (70)		1,01	3011303	. 101 301 1003	2011043		333	.54	Risk ratio (95% CI):	Moderate
Vomiting	6 ^{1, 2, 6, 10-}		Not						2.14 (0.77, 5.91)	
(%)	12	RCT	serious	Not serious	Serious ^b	Not serious	257	266	(p=0.14)	Moderate
V 1					-		<u> </u>		Risk ratio (95% CI):	
	9 ^{1, 2, 4-6, 8,}		Not						1.76 (1.01, 3.06)	
Diarrhea (%)	10-12	RCT	serious	Not serious	Serious ^b	Not serious	469	471	(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-		0		,				P		,
placement										
abdominal									Risk ratio (95% CI):	
pain/crampi	7 ^{1, 2, 4-6, 8,}		Not						2.14 (1.42, 3.23)	
ng (%)	10	RCT	serious	Serious ^a	Serious ^b	Not serious	388	393	(p=0.0003)*	Low
Adverse Even	ts									
									0/444 vs. 0/450;	
									Peto odds ratio	
Uterine									(95% CI): not	
perforation			Not						estimable due to 0	
(%)	7 ^{1, 3-6, 8, 10}	RCT	serious	Not serious	Very serious ^f	Not serious	444	450	events observed	Low
									9/388 vs. 10/392;	
									Peto odds ratio	
Vasovagal			Not						(95% CI): 0.94 (0.37,	
reaction (%)	6 ^{1-5, 10}	RCT	serious	Not serious	Serious ^{b,f}	Not serious	388	392	2.37) (p=0.89)†	Moderate
Patient Satisfa	action with F	Procedure	(assessed	before clinic disc	harge)					
Patient										
satisfaction										
with										
procedure									Mean difference	
(10 cm VAS			Not						(95% CI): 2.00 (-	
[mean])	2 ^{1, 4}	RCT	serious	Not serious	Serious ^b	Not serious	113	113	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

^aInconsistency is considered serious due to varying results among studies.

bImprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

^cRisk of bias is considered serious due to lack of information on randomization and allocation concealment processes in one study.

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

elmprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

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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

							Number			
	Number of	Study	Risk of				of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Lidocaine pa	racervical bl	ock vs. no	treatment							
Patient Pain										
Pain during										
tenaculum									Mean difference	
placement									(95% CI): -1.02 (-	
(10 cm VAS									2.08, 0.04)	
[mean])	11	RCT	Serious ^a	Not serious	Serious ^{b,c}	Not serious	26	24	(p=0.06)	Low
Pain during										
IUD									Mean difference	
placement									(95% CI): -0.78 (-	
(10 cm VAS	2 ^{1, 2}	рст	Serious ^{a,d}	Natassia	Serious ^b	Not coming	CO	70	1.37, -0.18)	1
[mean]) Highest	Ζ'	RCT	Serious	Not serious	Serious	Not serious	68	70	(p=0.01)	Low
level of										
pain after										
IUD										
placement										
and before										
clinic									Mean difference	
discharge									(95% CI): -0.55 (-	
(10 cm VAS									1.36, 0.27)	
[mean])	21, 2	RCT	Serious ^{a,d}	Not serious	Serious ^b	Not serious	68	70	(p=0.19)	Low
									Median (range):	
									4 (0-6) for	
Pain during									lidocaine group	
tenaculum									vs. 7 (5-8) for	
placement									comparison	
(10 cm VAS	43	D.C.T.			c · cf		2.4	24	group; median	1.
[median])	1 ³	RCT	Serious ^e	Not serious	Serious ^{c,f}	Not serious	34	31	difference: 3.0	Low

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									(no pairwise test conducted)	
Pain during IUD placement (10 cm VAS									Median (range): 2 (0-5) for lidocaine group vs. 6 (3-7) for comparison; median difference: -4.0 (no pairwise test	
[median])	1 ³	RCT	Serious ^e	Not serious	Serious ^{c,f}	Not serious	34	31	conducted)	Low
Highest level of pain after IUD placement and before clinic discharge (10 cm VAS [median]) Moderate or severe	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
pain during tenaculum placement (%) Moderate or severe pain during	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
IUD placement (%)	14	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 Adj				meonoistency	mprecision	munectness	treatment	Companison	Lilect	certainty
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 Su	ıccess	T	T	I	T	I	T T		Risk ratio (95%	T
Placement success (%)	2 ^{1, 2}	RCT	Serious ⁱ	Not serious	Serious ^c	Not serious	68	70	CI): 0.99 (0.96, 1.04) (p=0.80)	Low
Adverse Ever	nts									
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 par	racervical bl	ock vs. pla	cebo/sham	block					,	,
Patient Pain										
Pain during tenaculum placement (10 cm VAS									Median (range): 4 (0-6) for lidocaine group vs. 7 (4-9) for comparison group; median difference: -3.0 (no pairwise test	
[median])	1 ³	RCT	Serious ^e	Not serious	Serious ^{c,f}	Not serious	34	31	conducted)	Low

	Number		2116				Number of	Number of		
0	of	Study	Risk of	In a suciation and	lua unua aini a u	In diagram and	patients:	patients:	Title at	Cautaintu
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect Median (range):	Certainty
									2 (0-5) for	
									lidocaine group	
									vs. 6 (2-7) for	
Pain during									comparison	
IUD									group; median	
placement									difference: -4.0	
(10 cm VAS									(no pairwise test	
[median])	1 ³	RCT	Serious ^e	Not serious	Serious ^{c,f}	Not serious	34	31	conducted)	Low
Highest										
level of									Median (range):	
pain after									1 (0-4) for	
IUD									lidocaine group	
placement									vs. 4 (1-6) for	
and before									comparison	
clinic									group; median	
discharge (10 cm VAS									difference: -3.0	
[median])	1 ³	RCT	Serious ^e	Not serious	Serious ^{c,f}	Not serious	34	31	(no pairwise test conducted)	Low
[IIIeulali])	Т	KC1	Serious	Not serious	Serious	Not serious	34	31	Median: 2.35 for	LOW
									lidocaine group	
									vs. 6.00 for	
Pain during									comparison	
tenaculum									group (p=0.001);	
placement									median	
(10 cm VAS									difference: -	
[median])	1 ⁵	RCT	Serious ^k	Not serious	Serious ^{c,f}	Not serious	47	48	3.65*	Low
									Median: 3.00 for	
Pain during									lidocaine group	
IUD									vs. 7.15 for	
placement									comparison	
(10 cm VAS	45	B.C=			6		4-	4.5	group (p<0.001);	<u> </u>
[median])	1 ⁵	RCT	Serious ^k	Not serious	Serious ^{c,f}	Not serious	47	48	median	Low

	Number	6. 1	D: 1 (Number of	Number of		
Outcome	of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	patients: treatment	patients: comparison	Effect	Certainty
Outcome	Studies	uesigii	Dias	inconsistency	imprecision	munectness	treatment	Companison	difference: -	Certainty
									4.15*	
Highest										
level of										
pain after										
IUD									Median: 0.50 for	
placement									lidocaine group	
and before									vs. 2.90 for	
clinic									comparison	
discharge									group (p-value	
(10 cm VAS					_				NR); median	
[median])	1 ⁵	RCT	Serious ^k	Not serious	Serious ^{f,g}	Not serious	47	48	difference: -2.4	Low
									Median (IQR):	
									1.5 (0.6-2.4) for	
									lidocaine group	
Pain during tenaculum									vs. 1.0 (0.4-1.9) for comparison	
placement									group (p=0.268);	
(10 cm VAS			Not						median	
[median])	1 ⁶	RCT	serious	Not serious	Serious ^{c,f}	Not serious	33	31	difference: 0.5	Low
[σα.α]/			33.1343						Median (IQR):	2011
									3.3 (1.0-5.6) for	
									lidocaine group	
Pain during									vs. 5.4 (3.3-7.5)	
IUD									for comparison	
placement									group (p=0.002);	
(10 cm VAS			Not						median	
[median])	1 ⁶	RCT	serious	Not serious	Serious ^{c,f}	Not serious	33	31	difference: -2.1*	Low
Highest									Median (IQR):	
level of									1.2 (0.6-2.7) for	
pain after IUD			Not						lidocaine group	
placement	1 ⁶	RCT	Not serious	Not serious	Serious ^{c,f}	Not serious	33	31	vs. 2.7 (1.5-5.0) for comparison	Low
piacement	T.	rc i	serious	INOL SELIOUS	Sellous.	INOL SELIOUS	၁၁	21	TOT COTTIPATISON	LUW

							Number			
	Number						of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
and before				_	_			_	group (p=0.005);	
clinic									median	
discharge									difference: -1.5*	
(10 cm VAS										
[median])										
Need for Adju	unctive Plac	ement Me	asures							
									Risk ratio (95%	
Cervical									CI): 0.77 (0.22,	
dilation (%)	3 ^{3, 5, 6}	RCT	Serious ^k	Not serious	Serious ^{b,c}	Not serious	114	109	2.74) (p=0.69)	Low
									Risk ratio (95%	
Analgesia			Not						CI): 0.47 (0.20,	
(%)	1 ⁶	RCT	serious	Not serious	Serious ^{b,c}	Not serious	33	31	1.10) (p=0.08)	Moderate
Placement Su	iccess		1	1		T	1			
									Risk ratio (95%	
Placement	5.6								CI): 1.00 (0.97,	
success (%)	2 ^{5, 6}	RCT	Serious ^k	Not serious	Serious ^c	Not serious	80	79	1.03) (p=1.00)	Low
Side Effects			T	1	T	T	T			T
									Peto odds ratio	
									(95% CI): not	
									estimable due to	
	-								0 events	
Tinnitus (%)	1 ⁵	RCT	Serious ^k	Not serious	Serious ^c	Not serious	47	48	observed	Low
									Peto odds ratio	
									(95% CI): not	
									estimable due to	
Vomiting			Not						0 events	
(%)	1 ⁶	RCT	serious	Not serious	Serious ^c	Not serious	33	31	observed	Moderate
									Risk ratio (95%	
Dizziness			Not						CI): 1.17 (0.53,	
(%)	1 ⁶	RCT	serious	Not serious	Serious ^{b,c}	Not serious	33	31	2.59) (p=0.69)	Moderate
Adverse Even	its									

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									0/81 vs. 0/78;	
									Peto odds ratio	
									(95% CI): not	
Uterine									estimable due to	
perforation					Very				0 events	
(%)	23,5	RCT	Serious ^l	Not serious	serious ^c	Not serious	81	78	observed	Very low
									1/34 vs. 2/30;	
									Peto odds ratio	
Vasovagal									(95% CI): 0.44	
reaction	4.2	D.O.T.			Very			2.0	(0.04, 4.41)	, ,
(%)	1 ³	RCT	Serious ^e	Not serious	serious ^{b,c}	Not serious	34	30	(p=0.49)	Very low
Patient Satis	action with	Procedure	1	ı	T	ı	ı	ı	T	ı
Satisfied										
with IUD										
placement									Risk ratio (95%	
procedure	1 ⁵	рст	Cariaciak	Neterious	CariavaC	Nich comicus	47	40	CI): 1.00 (0.88,	1
(%) Would	1°	RCT	Serious ^k	Not serious	Serious ^c	Not serious	47	48	1.13) (p=0.98)	Low
									Dick ratio (OF9/	
recommen									Risk ratio (95%	
d an IUD to a friend (%)	1 ⁵	RCT	Serious ^k	Not serious	Serious ^c	Not serious	47	48	CI): 1.07 (0.93, 1.24) (p=0.36)	Low
Would	1.	KCI	Serious	Not serious	Serious	Not serious	47	40	1.24) (p=0.36)	LOW
choose the										
same pain										
control										
method for									Risk ratio (95%	
a future			Not						CI): 1.25 (0.79,	
IUD (%)	1 ⁶	RCT	serious	Not serious	Serious ^{b,c}	Not serious	33	31	1.98) (p=0.33)	Moderate
Would							-		, , , ,	
recommen										
d pain									Risk ratio (95%	
control			Not						CI): 1.47 (0.99,	
method to	1 ⁶	RCT	serious	Not serious	Serious ^{b,c}	Not serious	33	31	2.17) (p=0.05)	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
a friend for										
IUD										
placement										
(%)										
Lidocaine inti	racervical bl	ock vs. no	treatment							
Patient Pain										
Pain during										
tenaculum									Mean difference	
placement									(95% CI): -2.00 (-	
(10 cm VAS			Not						2.64, -1.36)	
[mean])	1 ⁷	RCT	serious	Not serious	Serious ^b	Not serious	99	101	(p<0.00001)*	Moderate
Pain during										
IUD									Mean difference	
placement									(95% CI): -1.50 (-	
(10 cm VAS			Not						2.28, -0.72)	
[mean])	17	RCT	serious	Not serious	Serious ^b	Not serious	99	101	(p=0.0002)*	Moderate
Provider Ease	of Placeme	ent								
"Usual"									Risk ratio (95%	
placement			Not						CI): 1.13 (1.02,	
(%)	17	RCT	serious	Not serious	Serious ^b	Not serious	99	102	1.25) (p=0.02)	Moderate
Need for Adju	unctive Plac	ement Me	asures							
									Risk ratio (95%	
Cervical			Not						CI): 0.43 (0.16,	
dilation (%)	17	RCT	serious	Not serious	Serious ^{b,c}	Not serious	99	102	1.17) (p=0.10)	Moderate
Placement Su	ıccess									
									Risk ratio (95%	
Placement			Not						CI): 1.01 (0.98,	
Success (%)	17	RCT	serious	Not serious	Serious ^c	Not serious	99	102	1.04) (p=0.49)	Moderate
Adverse Even	its									
Uterine									0/99 vs. 0/102;	
perforation			Not		Very				Peto odds ratio	
(%)	17	RCT	serious	Not serious	serious ^c	Not serious	99	102	(95% CI): not	Low

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									estimable due to	
									0 events	
									observed	
									1/99 vs. 7/102;	
									Peto odds ratio	
Vasovagal									(95% CI): 0.22	
reaction	_		Not						(0.05, 0.89)	
(%)	17	RCT	serious	Not serious	Serious ^{b,c}	Not serious	99	102	(p=0.03)*	Moderate
Lidocaine int	racervical b	lock vs. pla	cebo/sham	block						
Patient Pain										
Pain during										
tenaculum									Mean difference	
placement									(95% CI): -2.60 (-	
(10 cm VAS			Not						3.24, -1.96)	
[mean])	1 ⁷	RCT	serious	Not serious	Serious ^b	Not serious	99	100	(p<0.00001)*	Moderate
Pain during										
IUD									Mean difference	
placement									(95% CI): -2.30 (-	
(10 cm VAS	4.7	207	Not		. h			400	2.98, -1.62)	
[mean])	17	RCT	serious	Not serious	Serious ^b	Not serious	99	100	(p<0.00001)*	Moderate
Provider Eas	e of Placeme	ent		ı	1		1		T .	T
"Usual"									Risk ratio (95%	
placement	. 7		Not						CI): 1.08 (0.99,	
(%)	17	RCT	serious	Not serious	Not serious	Not serious	99	101	1.18) (p=0.10)	High
Need for Adj	unctive Plac	ement Me	asures	1	1				I	1
									Risk ratio (95%	
Cervical	_		Not						CI): 0.57 (0.20,	
dilation (%)	17	RCT	serious	Not serious	Serious ^{b,c}	Not serious	99	101	1.63) (p=0.29)	Moderate
Placement S	uccess	1			1				1	1
									Risk ratio (95%	
Placement	_		Not						CI): 1.01 (0.98,	
Success (%)	1 ⁷	RCT	serious	Not serious	Serious ^c	Not serious	99	101	1.04) (p=0.48)	Moderate

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

^aRisk of bias is considered serious due to lack of information on the allocation concealment processes in one study.

^bImprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

^cImprecision is considered serious due to the small sample size.

^dRisk 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.

eRisk of bias is considered serious due to lack of information on randomization and allocation concealment processes in the study.

fImprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

^gRisk 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.

^hRisk 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.

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.

^jRisk 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.

^kRisk 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

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Topical lidoc	aine vs. plac	ebo/no tr	eatment							
Patient Pain										
Pain during										
tenaculum									Mean difference	
placement									(95% CI): -1.69 (-	
(10 cm VAS			Not						2.53, -0.85)	
[mean])	41-4	RCT	serious	Serious ^a	Serious ^d	Not serious	201	201	(p<0.0001)*	Low
Pain during										
IUD									Mean difference	
placement									(95% CI): -0.97 (-	
(10 cm VAS			Not						1.69, -0.24)	
[mean])	8 ¹⁻⁸	RCT	serious	Serious ^a	Serious ^d	Not serious	540	541	(p=0.009)	Low
Highest										
level of										
pain after										
IUD										
placement										
and before										
clinic									Mean difference	
discharge									(95% CI): -0.65 (-	
(10 cm VAS			Not						0.94, -0.36)	
[mean])	2 ^{2, 3}	RCT	serious	Not serious	Not serious	Not serious	110	110	(p<0.0001)	High
Moderate										
or severe										
pain during										
tenaculum									Risk ratio (95%	
placement									CI): 0.62 (0.36,	
(%)	3 ^{b,9, 10}	RCT	Serious ^c	Not serious	Serious ^d	Not serious	166	111	1.05) (p=0.08)	Low
Moderate									Risk ratio (95%	
or severe									CI): 0.76 (0.50,	
pain during	3 ^{b,9, 10}	RCT	Serious ^c	Serious ^a	Serious ^d	Not serious	166	112	1.18) (p=0.22)	Very low

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
IUD										
placement										
(%)										
Highest level of										
pain after										
IUD										
placement										
and before										
clinic										
discharge										
(% with 10									Risk ratio (95%	
cm VAS			Not						CI): 0.64 (0.26,	
score ≥4)	1 ¹⁰	RCT	serious	Not serious	Serious ^d	Not serious	62	62	1.53) (p=0.31)	Moderate
Pain during									Median (IQR):	
tenaculum									3.2 (1.8-5.4) vs.	
placement									5.6 (2.6-7.5)	
(10 cm VAS			Not						(p=0.02); median	
[median])	1 ¹¹	RCT	serious	Not serious	Serious ^{e,f}	Not serious	30	29	difference: -2.4*	Moderate
Pain during									Median (IQR):	
IUD									6.1 (5.3-7.1) vs.	
placement									6.9 (6.3-8.0)	
(10 cm VAS	44		Not		. 6				(p=0.06); median	_
[median])	111	RCT	serious	Not serious	Serious ^{e,f}	Not serious	30	29	difference: -0.8	Moderate
Highest										
level of										
pain after										
IUD placement										
and before									Median (IQR):	
clinic									2.9 (1.1-5.7) vs.	
discharge									3.8 (1.8-6.2)	
(10 cm VAS			Not						(p=0.28); median	
[median])	1 ¹¹	RCT	serious	Not serious	Serious ^{e,f}	Not serious	30	29	difference: -0.9	Moderate

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Pain during					-			-	Median (IQR): 2	_
tenaculum									(2-3) vs. 4 (3-6)	
placement									(p=0.0001);	
(10 cm VAS			Not						median	
[median])	112	RCT	serious	Not serious	Serious ^f	Not serious	60	60	difference: -2.0*	Moderate
Pain during									Median (IQR): 3	
IUD									(2-3) vs. 6.5 (4-8)	
placement									(p=0.0001);	
(10 cm VAS			Not						median	
[median])	1 ¹²	RCT	serious	Not serious	Serious ^f	Not serious	60	60	difference: -3.5*	Moderate
Highest										
level of										
pain after										
IUD										
placement									M = -1: (10D) - 2	
and before									Median (IQR): 2	
clinic discharge									(1-2) vs. 3.5 (2-6) (p=0.0001);	
(10 cm VAS			Not						median	
[median])	1 ¹²	RCT	serious	Not serious	Serious ^f	Not serious	60	60	difference: -1.5*	Moderate
Pain during	1	ICI	3611003	Not serious	Jerious	Not serious	00	00	difference1.5	Wioderate
tenaculum									Median (range):	
placement									4 (0-10) vs. 4 (0-	
(10-point									10) (p=0.15);	
scale			Not						median	
[median])	1 ¹³	RCT	serious	Not serious	Serious ^f	Not serious	100	99	difference: 0.0	Moderate
Pain during										
IUD									Median (range):	
placement									5 (0-10) vs. 6 (0-	
(10-point									10) (p=0.16);	
scale			Not						median	
[median])	1 ¹³	RCT	serious	Not serious	Serious ^f	Not serious	100	99	difference: -1.0	Moderate
Pain during	_		Not						Median (range):	
tenaculum	1 ⁶	RCT	serious	Not serious	Serious ^f	Not serious	108	107	3.0 (0-8.6) vs. 3.8	Moderate

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
placement				,	•				(0-8.4) (p=0.15);	,
(10 cm VAS									median	
[median])									difference: -0.8	
Provider Ease	of Placeme	ent								
Provider										
ease of									Mean difference	
placement									(95% CI): -1.48 (-	
(10 cm VAS	3 ^{1, 3, 12}	5.07	Not		a . d		475	475	2.50, -0.45)	
[mean])	31, 3, 12	RCT	serious	Serious ^a	Serious ^d	Not serious	175	175	(p=0.005)	Low
Easy			Not						Risk ratio (95%	
placement	1^{11}	RCT	Not serious	Not serious	Serious ^{d,e}	Not serious	30	28	CI): 1.35 (0.99, 1.84) (p=0.06)	Moderate
(%) Provider		KCI	serious	Not serious	Serious	Not serious	30	20	Median (range):	Moderate
ease of									0.9 (0.1-9.8) vs.	
placement									0.9 (0.1-9.6)	
(10 cm VAS			Not						(p=0.84); median	
[median])	1 ⁶	RCT	serious	Not serious	Serious ^f	Not serious	108	107	difference: 0.0	Moderate
Need for Adj	unctive Plac	ement Me								
									Risk ratio (95%	
Cervical			Not						CI): 0.38 (0.04,	
dilation (%)	2 ^{7, 11}	RCT	serious	Serious ^a	Serious ^{d,e}	Not serious	130	129	3.62) (p=0.40)	Low
									1/122 vs. 6/122;	
									Peto odds ratio	
									(95% CI): 0.22	
Analgesia			Not						(0.05, 1.02)	
(%)	2 ^{10, 12}	RCT	serious	Not serious	Serious ^d	Not serious	122	122	(p=0.05)†	Moderate
									1/100 vs. 1/100;	
									Peto odds ratio	
Local									(95% CI): 1.00	
anesthesia	- 7		Not						(0.06, 16.10)	
(%)	17	RCT	serious	Not serious	Serious ^{d,e}	Not serious	100	100	(p=1.00)	Moderate
Placement Su	iccess									

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

^aInconsistency is considered serious due to varying results among studies.

^bOne study is included twice in the analysis because it examined two interventions.

^cRisk 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.

^dImprecision is considered serious or very serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

^eImprecision is considered serious or very serious due to the small sample size.

fImprecision 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:	Effect	Certainty
Intrauterine				meonsistency	mprecision	indirectiness	treatment	companison	Lileat	Certainty
Patient Pain	mound to the	or places	<u> </u>							
Pain during IUD placement										
(patient reported) (10 cm VAS or 9-point scale [mean])	3 a,1, 2	RCT	Seriou s ^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	3**	RCI	Seriou	NOT SELIOUS	Not serious	NOT SELIOUS	96	36	Mean difference (95% CI): 0.07 (-	Moderate
[mean]) Pain during tenaculum placement (10 cm VAS	2 ^{a,1}	RCT	s ^b	Not serious	Not serious	Not serious	78	38	0.18, 0.33) (p=0.57) Median (IQR): 2.2 (0.9-3.4) vs. 2.4 (0.3-4.5) (p=0.487); median difference: -	Moderate
[median]) Pain during IUD placement (10 cm VAS	13	RCT	serious Not	Not serious	Serious ^{c,d}	Not serious	41	40	0.4 Median (IQR): 4.8 (3.1-5.8) vs. 5.9 (3.3- 7.5) (p=0.062); median difference: -	Moderate
[median])	1 ³	RCT	serious	Not serious	Serious ^{c,d}	Not serious	41	40	1.1	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Highest										
level of										
pain after										
IUD										
placement										
and before										
clinic									Mean difference	
discharge									(95% CI): -1.59 (-	
(10 cm VAS	4.1	D.O.T.	Not				100	400	2.28, -0.90)	
[mean])	14	RCT	serious	Not serious	Serious ^e	Not serious	106	103	(p<0.00001)*	Moderate
Highest										
level of										
pain after IUD										
placement										
and before									Median (IQR): 1.3	
clinic									(0.5-2.5) vs. 1.3 (0.6-	
discharge									3.7) (p=0.545);	
(10 cm VAS			Not						median difference:	
[median])	1 ³	RCT	serious	Not serious	Serious ^{c,d}	Not serious	41	40	0.0	Moderate
Provider Ease	of Placeme	ent						_		
Easy									97% vs. 95%; Risk	
placement			Seriou						ratio (95% CI): 1.03	
(%)	2 ^{a,1}	RCT	s ^b	Not serious	Not serious	Not serious	78	38	(0.95, 1.12) (p=0.51)	Moderate
Need for Adj	unctive Plac	ement Mo	easures							
•									15% vs 31%; Risk	
									ratio (95% CI): 0.51	
Analgesia			Not						(0.30, 0.85)	
(%)	14	RCT	serious	Not serious	Serious ^e	Not serious	110	108	(p=0.01)*	High
Placement Su	ıccess									
									98% vs 96%; Risk	
Placement			Not						ratio (95% CI): 1.03	
success (%)	5 ^{a,1-4}	RCT	serious	Not serious	Not serious	Not serious	249	210	(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 Satisf	faction with	Procedur	e							
Patient satisfaction (5-point									Mean difference	
scale			Seriou						(95% CI): -0.09 (-	
[mean])	2 ^{a,1}	RCT	s ^b	Not serious	Serious ^c	Not serious	78	38	0.44, 0.26) (p=0.62)	Low
Would choose an IUD for										
contracepti									95% vs. 93%; Risk	
on again			Not						ratio (95% CI): 1.03	
(%)	1 ³	RCT	serious	Not serious	Serious ^c	Not serious	41	40	(0.92, 1.15) (p=0.63)	Moderate
Would recommen d an IUD to			Not						98% vs. 95%; Risk ratio (95% CI): 1.03	
a friend (%)	1 ³	RCT	serious	Not serious	Serious ^c	Not serious	41	40	(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.

^aOne study is included twice in the analysis because it examined two interventions.

^bRisk of bias is considered serious due to lack of information on allocation concealment processes in one study which is included twice in the analysis.

^cImprecision is considered serious due to the small sample size.

^dImprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

^eImprecision 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.

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
NSAIDs vs. pl	acebo									
Patient Pain Pain during			I	T	T	T				T
tenaculum									Mean difference	
placement									(95% CI): -0.24 (-	
(10 cm VAS			Not						0.70, 0.22)	
[mean])	2 ^{1, 2}	RCT	serious	Not serious	Not serious	Not serious	114	107	(p=0.31)	High
Pain during			3011003	1101 3011043	1100 3011043	1100 30110 43		107	(β 0.01)	
IUD										
placement										
(patient-										
reported)									Mean difference	
(10 cm VAS									(95% CI): -0.95 (-	
or scale									1.76, -0.14)	
[mean])	5 ¹⁻⁵	RCT	Serious ^a	Serious ^b	Serious ^c	Not serious	224	215	(p=0.02)	Very low
Pain during										
IUD										
placement										
(provider-									Mean difference	
reported)									(95% CI): -0.11 (-	
(10 cm VAS	1 ⁵	DCT	Serious ^d	Natassia	Cominance	Natassia	40	20	0.37, 0.15)	1
[mean]) Highest	T,	RCT	Serious	Not serious	Serious ^e	Not serious	40	38	(p=0.40)	Low
level of										
pain after										
IUD										
placement									Mean difference	
and before									(95% CI): -0.52 (-	
clinic			Not						0.84, -0.20)	
discharge	2 ^{2, 3}	RCT	serious	Not serious	Not serious	Not serious	105	106	(p=0.001)	High

Outcome	Number of	Study	Risk of Bias		l	lo dino sha so	Number of patients:	Number of patients:	F#Fe et	Containtu
Outcome (10 cm VAS	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
[mean])										
Pain during tenaculum placement (10 cm VAS	16		Not						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:	
[median])	16	RCT	serious	Not serious	Serious ^{e,f}	Not serious	33	34	-1.9	Moderate
Pain during IUD placement (10 cm VAS			Not						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:	
[median])	1 ⁶	RCT	serious	Not serious	Serious ^{e,f}	Not serious	33	34	-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	1	Ref	Serious	Not serious	Serious	NOT SELIOUS	33	34	Median: 3.7 for NSAID group vs. 3.2 for placebo group (p=0.97);	Woderate
(10 cm VAS	47	DOT	Not		G · f		50	60	median difference:	
[median])	1 ⁷	RCT	serious	Not serious	Serious ^f	Not serious	58	60	0.5	Moderate

	Number						Number of	Number of		
0	of	Study	Risk of			to diameter and	patients:	patients:	F66 A	Contointe
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect Median: 6.9 for	Certainty
Pain during									NSAID group vs.	
IUD									6.6 for placebo	
placement									group (p=0.89);	
(10 cm VAS			Not						median difference:	
[median])	1 ⁷	RCT	serious	Not serious	Serious ^f	Not serious	58	60	0.3	Moderate
Highest	_									
level of										
pain after										
IUD										
placement									Median: 1.7 for	
and before									NSAID group vs.	
clinic									2.6 for placebo	
discharge									group (p=0.01);	
(10 cm VAS	_		Not						median difference:	
[median])	17	RCT	serious	Not serious	Serious ^f	Not serious	58	60	-0.9	Moderate
									Median (IQR): 2 (1-	
Pain during									3) for NSAID group	
tenaculum									vs. 4 (3-5) for	
placement (10 cm VAS			Not						placebo group	
[median])	18	RCT	serious	Not serious	Serious ^{e,f}	Not serious	48	46	(p<0.001); median difference: -2.0*	Moderate
[IIIeulali])	1	KCI	serious	Not serious	Serious	Not serious	40	40	Median (IQR): 2.3	Moderate
Pain during									(2-3) for NSAID	
IUD									group vs. 5 (3-7)	
placement									for placebo group	
(10 cm VAS			Not						(p<0.001); median	
[median])	18	RCT	serious	Not serious	Serious ^{e,f}	Not serious	48	46	difference: -2.7*	Moderate
Highest									Median (IQR): 1 (1-	
level of									1.5) for NSAID	
pain after									group vs. 2 (1-2)	
IUD									for placebo group	
placement			Not						(p<0.001); median	
and before	18	RCT	serious	Not serious	Serious ^{e,f}	Not serious	48	46	difference: -1.0	Moderate

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
clinic		0		,						,
discharge										
(10 cm VAS										
[median])										
Highest										
level of										
pain after										
IUD										
placement									Median (IQR): 4	
and before									(1.5-6) for NSAID	
clinic									group vs. 4 (2-6)	
discharge									for placebo group	
(10 cm VAS	40	DOT	Not		C · f		65	65	(p=0.873); median	
[median])	19	RCT	serious	Not serious	Serious ^f	Not serious	65	65	difference: 0.0	Moderate
Pain during IUD									Median: 3.3 for	
placement									NSAID group vs. 2.5 for placebo	
(10-point									group (p-value	
scale			Not						NR); median	
[median])	1 ¹⁰	RCT	serious	Not serious	Serious ^{e,f}	Not serious	27	28	difference: 0.8	Moderate
[mealan])		ill.	3011003	1401 3011003	3611043	1400 3011003	2,	20	Median: 1.0 for	Wioderate
Pain during									NSAID group vs.	
IUD									1.0 for placebo	
placement									group (p-value	
(10 cm VAS			Not						NR); median	
[median])	1 ¹¹	RCT	serious	Not serious	Serious ^f	Not serious	1011	1008	difference: 0.0	Moderate
Highest										
level of									Median (range):	
pain after									3.8 (0-10) for	
IUD									NSAID group vs.	
placement									4.2 (0-10) for	
and before									placebo group	
clinic	. 12		Not				45.		(p=0.50); median	
discharge	112	RCT	serious	Not serious	Serious ^f	Not serious	101	101	difference: -0.4	Moderate

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

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									Peto odds ratio	
									(95% CI): 0.14	
Vomiting	-467		Not						(0.01, 2.23)	
(%)	3 ^{4, 6, 7}	RCT	serious	Not serious	Serious ^{c,e}	Not serious	126	128	(p=0.16) [†]	Moderate
									Peto odds ratio	
									(95% CI): 0.67	
Dizziness	4.6								(0.11, 4.12)	
(%)	2 ^{4, 6}	RCT	Serious ^g	Not serious	Serious ^{c,e}	Not serious	68	68	(p=0.67)*	Low
									Risk ratio (95% CI):	
Drowsiness	_		Not						1.03 (0.07, 15.80)	
(%)	1 ⁶	RCT	serious	Not serious	Serious ^{c,e}	Not serious	33	34	(p=0.98)	Moderate
Adverse Ever	nts									
									0/118 vs. 0/116;	
									Peto odds ratio	
Uterine									(95% CI): not	
perforation			Not		Very				estimable due to 0	
(%)	2 ^{2,8}	RCT	serious	Not serious	serious ^{c,e}	Not serious	118	116	events observed	Low
									2/176 vs. 3/176;	
									Peto odds ratio	
Vasovagal									(95% CI): 0.68	
reaction			Not		Very				(0.11, 4.08)	
(%)	3 ^{2, 7, 8}	RCT	serious	Not serious	serious ^{c,e}	Not serious	176	176	(p=0.68)†	Low
Patient Satisf	action with	Placemer	nt							
Patient										
satisfaction										
(10 cm VAS									Standardized mean	
or 5-point									difference (95%	
scale			Not						CI): 0.54 (-0.05,	
[mean])	3 ^{2, 5, 8}	RCT	serious	Serious ^b	Not serious	Not serious	158	154	1.14), p=0.07	Moderate
Very									Risk ratio (95% CI):	
satisfied			Not						1.13 (0.70, 1.80)	
(%)	1 ⁶	RCT	serious	Not serious	Serious ^{c,e}	Not serious	33	33	(p=0.62)	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Unpleasant	Studies	ucsign	Dias	inconsistency	imprecision	maneethess	treatment	companison	Lilect	certainty
/very									Risk ratio (95% CI):	
unpleasant									0.17 (0.07, 0.38)	
(%)	14	RCT	Serious ^g	Not serious	Serious ^e	Not serious	34	34	(p<0.0001)*	Low
(70)			0011000		00.100.0		0.	<u> </u>	Median (IQR): 9.2	
									(8.3-9.9) for NSAID	
									group vs. 9.1 (8.2-	
Patient									9.8) for placebo	
satisfaction									group (p=0.56);	
(10 cm VAS			Not						median difference:	
[median])	17	RCT	serious	Not serious	Serious ^{e,f}	Not serious	58	60	0.1	Moderate
NSAID + lidoo	aine vs. pla	cebo								
Patient Pain										
Pain during										
tenaculum									Mean difference	
placement									(95% CI): -0.67 (-	
(10 cm VAS			Not						1.10, -0.24),	
[mean])	1 ¹³	RCT	serious	Not serious	Serious ^e	Not serious	45	45	p=0.002	Moderate
Pain during										
IUD										
placement										
(patient-									Mean difference	
reported)									(95% CI): -0.72 (-	
(10 cm VAS	F 12								1.14, -0.29)	
[mean])	2 ^{5, 13}	RCT	Serious ^d	Not serious	Not serious	Not serious	84	83	(p=0.001)	Moderate
Pain during										
IUD										
placement									NA	
(provider-									Mean difference	
reported)									(95% CI): 0.18 (-	
(10 cm VAS	1 ⁵	DCT	Camiacod	Nat assiste	Cariarra	Not sovieve	20	20	0.08, 0.44)	
[mean])		RCT	Serious ^d	Not serious	Serious ^e	Not serious	39	38	(p=0.17)	Low
Provider Ease	of Placeme	ent								

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Provider									NA IIII	
ease of									Mean difference	
placement (10 cm VAS			Not						(95% CI): -0.22 (- 0.95, 0.51)	
[mean])	1 ¹³	RCT	serious	Not serious	Serious ^e	Not serious	45	45	(p=0.56)	Moderate
Easy	1	KCI	serious	Not serious	Serious	Not serious	43	43	Risk ratio (95% CI):	iviouerate
placement									1.03 (0.94, 1.13)	
(%)	1 ⁵	RCT	Serious ^d	Not serious	Serious ^e	Not serious	39	38	(p=0.54)	Low
` ′		I NC1	Jerious	NOT SELIOUS	3611003	Not serious	35	36	(μ=0.54)	LOW
Placement Su	access						<u> </u>		Bick ratio (OE9/ CI):	1
Placement									Risk ratio (95% CI): 1.01 (0.97, 1.04),	
success (%)	2 ^{5, 13}	RCT	Serious ^d	Not serious	Serious ^e	Not serious	84	84	p=0.71	Low
` ,	_	INCI	Jenous	Not serious	Serious	Not serious	04	04	μ=0.71	LOW
Adverse Ever	115		1		I	I	Ι		0/45 vs. 0/45; Peto	1
									odds ratio (95%	
Uterine									CI): not estimable	
perforation			Not		Very				due to 0 events	
(%)	1 ¹³	RCT	serious	Not serious	serious ^e	Not serious	45	45	observed	Low
(70)		ile:	3011043	1401 3011003	3011003	110t Scribus	43	73	1/45 vs. 2/45; Peto	2000
Vasovagal									odds ratio (95%	
reaction			Not		Very				CI): 0.51 (0.05,	
(%)	1 ¹³	RCT	serious	Not serious	serious ^{d,e}	Not serious	45	45	4.99) (p=0.56)	Low
Patient Satist	faction with	Placemer	nt						, , , ,	
Patient										
satisfaction									Mean difference	
(5-point									(95% CI): -0.04 (-	
scale									0.43, 0.35)	
[mean])	1 ⁵	RCT	Serious ^d	Not serious	Serious ^e	Not serious	39	38	(p=0.84)	Low
NSAID + mus	cle relaxant	vs. placel	00							
Patient Pain										
Pain during									Mean difference	
IUD	114	RCT	Serious ^h	Not serious	Serious ^{c,e}	Not serious	31	25	(95% CI): -2.00 (-	Low

							Number			
	Number						of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
placement	Studies	ucsign	Dias	inconsistency	Imprecision	manectness	treatment	companison	2.77, -1.23)	certainty
(10 cm VAS									(p<0.00001)*	
[mean])									(p (0.00001)	
Highest										
level of										
pain after										
IUD										
placement										
and before										
clinic									Mean difference	
discharge									(95% CI): -0.73 (-	
(10 cm VAS									1.15, -0.31)	
[mean])	114	RCT	Serious ^h	Not serious	Serious ^e	Not serious	31	25	(p=0.0006)	Low
Placement Su	ıccess	I	ı	T						
									Risk ratio (95% CI):	
Placement	4 1 /	D.O.T.	a . b				24	0.5	1.00 (0.93, 1.07)	
success (%)	114	RCT	Serious ^h	Not serious	Serious ^e	Not serious	31	25	(p=1.00)	Low
Tramadol vs.	placebo									
Patient Pain		T	T	1					T	1
Pain during										
IUD									Mean difference	
placement									(95% CI): -1.49 (-	
(10 cm VAS	2 ^{4, 15}	DCT	Camianai	C h	C: C	Nistra	5.0	66	3.71, 0.73)	Mamulann
[mean])	_	RCT	Serious ⁱ	Serious ^b	Serious ^c	Not serious	56	66	(p=0.19)	Very low
Provider Ease	e of Placeme	ent I		1					I	
Provider										
ease of placement									Mean difference	
(scale not									(95% CI): -1.80 (-	
described									2.71, -0.89)	
[mean])	1 ¹⁵	RCT	Serious ^j	Not serious	Serious ^{c,e}	Not serious	22	32	(p=0.0001)*	Low
Placement Su			20000	110000011000	1	1			NF 0.0001/	
riacement 30	10000									

							Number			
	Number						of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									Risk ratio (95% CI):	
Placement									1.00 (0.96, 1.05)	
success (%)	2 ^{4, 15}	RCT	Serious ⁱ	Not serious	Serious ^e	Not serious	56	66	(p=1.00)	Low
Side Effects										
									0/34 vs. 0/34; Peto	
									odds ratio (95%	
									CI): not estimable	
									due to 0 events	
Nausea (%)	14	RCT	Serious ^g	Not serious	Serious ^e	Not serious	34	34	observed	Low
									0/34 vs. 0/34; Peto	
									odds ratio (95%	
									CI): not estimable	
Vomiting									due to 0 events	
(%)	14	RCT	Serious ^g	Not serious	Serious ^e	Not serious	34	34	observed	Low
									0/34 vs. 0/34; Peto	
									odds ratio (95%	
									CI): not estimable	
Dizziness									due to 0 events	
(%)	14	RCT	Serious ^g	Not serious	Serious ^e	Not serious	34	34	observed	Low
Adverse Ever	nts									
									1/22 vs. 0/32; Peto	
Vasovagal									odds ratio (95%	
reaction			Not		Very				CI): (0.22, 628.58)	
(%)	1 ¹⁵	RCT	serious	Not serious	serious ^{c,e}	Not serious	22	32	(p=0.23)	Low
Patient Satis	faction with	Placemer	nt							
									6% of tramadol	
									group vs. 88% of	
Unpleasant									placebo group;	
/very									Risk ratio (95% CI):	
unpleasant									0.06 (0.02, 0.25)	
(%)	14	RCT	Serious ^g	Not serious	Serious ^e	Not serious	35	34	(p<0.0001)*	Low
Acetaminoph	nen vs. place	ebo								

Pain during	Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
IUD	Patient Pain				,		,				
Highest level of pain after	IUD placement (10 cm VAS	1 ¹⁶	RCT	Serious ^k	Not serious	Serious ^e	Not serious	30	46	(95% CI): -0.64 (- 1.14, -0.14)	Low
Placement Success Serious Seri	Highest level of pain after IUD placement and before clinic discharge		-						-	Mean difference (95% CI): -0.83 (-	
Placement success (%) 116 RCT Serious Not serious Seriouse Not serious 30 46 (p=1.00) Low Nitrous Oxide vs. placebo Patient Pain Highest level of pain after IUD placement and before clinic (10 cm VAS Not Serious Not Serious Not Serious Not Serious Not Serious 30 46 (p=1.00) Low	[mean])	1 ¹⁶	RCT	Serious ^k	Not serious	Serious ^e	Not serious	30	46	(p=0.0001)	Low
Placement success (%) 116 RCT Serious Not serious Seriouse Not serious 30 46 (p=1.00) Low Nitrous Oxide vs. placebo Patient Pair Highest level of pain after IUD placement and before clinic (10 cm VAS Not Serious Not Seri	Placement Su	ccess						1			
Patient Pain Highest level of pain after IUD placement and before clinic (10 cm VAS Not	success (%)			Serious ^j	Not serious	Serious ^e	Not serious	30	46	1.00 (0.95, 1.06)	Low
Highest level of pain after IUD placement and before clinic (10 (95% CI): -0.10 (-1.11, 0.91)	Nitrous Oxide	vs. placebo	o								
level of pain after IUD placement and before clinic (10 cm VAS Not Mean difference (95% Cl): -0.10 (-1.11, 0.91)				ı	ı		1			1	
placement and before clinic (10 cm VAS Not Mean difference (95% CI): -0.10 (-1.11, 0.91)	level of pain after										
	placement and before clinic (10			Not						(95% CI): -0.10 (-	
[[mean])	1 ¹⁷	RCT		Not serious	Serious ^e	Not serious	40	40	(p=0.85)	Moderate

	Number		511.6				Number of	Number of		
Outcome	of	Study	Risk of Bias	In a succiation and	lua unua aiai a u	In all we at we are	patients:	patients:	Effe et	Combolinatur
Outcome Provider	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
ease of										
placement									Mean difference	
(10 cm VAS			Not						(95% CI): 0.74 (-	
[mean])	1 ¹⁷	RCT	serious	Not serious	Serious ^{c,e}	Not serious	40	40	0.24, 1.72), p=0.14	Moderate
Placement S		itei	3011003	1100 3011003	3611003	Not serious		40	0.24, 1.72,, p=0.14	Wioderate
									Risk ratio (95% CI):	
Placement			Not						0.98 (0.91, 1.04)	
success (%)	1 ¹⁷	RCT	serious	Not serious	Serious ^e	Not serious	40	40	(p=0.48)	Moderate
Side Effects										
									0/40 vs. 5/40; Peto	
									OR (95% CI): 0.12	
	4-		Not						(0.02, 0.74)	
Nausea (%)	1 ¹⁷	RCT	serious	Not serious	Serious ^e	Not serious	40	40	(p=0.02)*	Moderate
									3/40 vs. 0/40; Peto	
5									OR (95% CI): 7.78	
Dizziness	1 ¹⁷	DCT	Not	Nick contour	C: C P	Nist souls	40	40	(0.79, 77.04)	N4
(%)		RCT	serious	Not serious	Serious ^{c,e}	Not serious	40	40	(p=0.08)	Moderate
Patient Satis	faction with	Placemer	nt 	l						
Satisfaction with pain										
manageme										
nt during										
IUD									Mean difference	
placement									(95% CI): 0.57 (-	
(10 cm VAS			Not						0.72, 1.86)	
[mean])	1 ¹⁷	RCT	serious	Not serious	Serious ^{c,e}	Not serious	40	40	(p=0.39)	Moderate
Satisfied or										
very										
satisfied										
with pain									Risk ratio (95% CI):	
manageme	4.7		Not						1.59 (1.04, 2.42)	
nt during	1 ¹⁷	RCT	serious	Not serious	Serious ^{c,e}	Not serious	40	40	(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

^aRisk 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.

^bInconsistency is considered serious due to varying results among studies.

^cImprecision is considered serious due to the confidence interval including clinically meaningful effects and non-clinically meaningful effects or no effects.

^dRisk of bias is considered serious due to lack of information on allocation concealment processes in one study.

^eImprecision is considered serious or very serious due to the small sample size.

fImprecision is considered serious due to lack of information on precision of difference between groups provided by the study.

^gRisk 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.

^hRisk of bias is considered serious due to lack of information on allocation concealment processes in one study.

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.

^{*}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.

^jRisk of bias is considered serious due to outcome assessors were aware of the assigned intervention received by study participants in one study.

^kRisk 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.

of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
	relaxants	vs. placeb	0						
								No significant difference in pain scores for 2 studies;	
		Not						median pain VAS scores for treatment group vs. placebo group in 1 study (2	
3 ^{a,1-3}	RCT	serious	Serious ^b	Not serious	Not serious	75	73	vs. 4 cm, p<0.0001)* No significant difference in pain scores for 2 studies; significantly lower median pain VAS scores for treatment	Moderate
221.3	DOT	Not				75	70	group vs. placebo group in 1 study (3 vs. 5.5 cm,	
		Not						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	Moderate Moderate
	oth muscle	3a,1-3 RCT	Not serious RCT serious Not serious	3a,1-3 RCT Serious Seriousb Not Seriousb Not Seriousb	3a,1-3 RCT Not serious Seriousb Not serious RCT Serious Seriousb Not serious Not serious Not serious Not serious	3a,1-3 RCT Serious Seriousb Not serious Not serious Not serious Seriousb Not serious Not serious Not serious Not serious Not serious Not serious	3a,1-3 RCT Not serious Serious Not serious Not serious 75 RCT Not serious Serious Not serious Not serious 75 Not serious Not serious 75	3a,1-3 RCT Serious Serious Not serious Not serious 75 73	Not serious Serious Serious Not serious Not serious 75 73 Not serious 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)* Not serious Not serious 75 73 vs. 4 cm, p<0.0001)* 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)* Not serious Not serious Not serious 75 73 p<0.0001)* No significantly lower median pain VAS scores for treatment group vs. placebo group in 1 study (3 vs. 5.5 cm, p<0.0001)* No significantly lower median pain VAS scores for treatment group vs. placebo group in 1 study (3 vs. 5.5 cm, p<0.0001)* No significantly lower median pain vAS scores for treatment group vs. placebo group in 1 study (2 ys. placebo group in 1 study (3 ys. placebo group in 1 st

							Number			
	Number						of	Number of		
	of	Churchy	Risk of							
0		Study				to diameter and	patients:	patients:	Eff	C
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Provider Ea	se of Place	ment	T	T		T	T			T
									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	
Easy									study (6.94±1.15 vs.	
place-			Not						4.74±1.38,	
ment	3 ^{a,1-3}	RCT	serious	Serious ^b	Not serious	Not serious	75	73	p<0.0001)*	Moderate
Need for Ad	ljunctive Pl	acement l	Measures							
									No significant	
Cervical			Not						difference between	
dilation	2 ^{a,1, 2}	RCT	serious	Not serious	Not serious	Not serious	25	23	groups	High
									1 participant had	
									paracervical block	
									but study did not	
									specify which group;	
									no participants	
Local			Not						received anesthetic	
anesthetic	2 ^{a,1, 2}	RCT	serious	Not serious	Not serious	Not serious	25	23	in other study	High
Placement S	Success									
									No significant	
									difference (all	
									participants had	
Place-									successful	
ment			Not						placements in both	
success	3 ^{a,1-3}	RCT	serious	Not serious	Not serious	Not serious	75	73	groups)	High
Patient Sati	sfaction wi	th Proced	ure							

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients:	Effect	Certainty
Outcome	Studies	acsign	Dias	inconsistency	Imprecision	manectness	treatment	companison	No significant	certainty
									difference in 2	
									studies; 1 study had	
									significantly higher	
									satisfaction scores in	
Patient									treatment group vs.	
satis-			Not						placebo group (92%	
faction	3 ^{a,1-3}	RCT	serious	Serious ^b	Not serious	Not serious	75	73	vs. 74%, p=0.003)	Moderate
Side Effects		.,							Γ	1
0.000									No significant	
			Not						difference between	
Nausea	2 ^{a,1, 2}	RCT	serious	Not serious	Not serious	Not serious	25	23	groups	High
									No significant	
			Not						difference between	
Vomiting	2 ^{a,1, 2}	RCT	serious	Not serious	Not serious	Not serious	25	23	groups	High
									No significant	
			Not						difference between	
Diarrhea	2 ^{a,1, 2}	RCT	serious	Not serious	Not serious	Not serious	25	23	groups	High
Adverse Ev	ents	-					-	_	10 11	<u> </u>
									1 study had 2	
									participants in	
									treatment group	
									experience vasovagal	
									reactions; none	
Vasovagal			Not						reported in other	
reaction	2 ^{a,1, 2}	RCT	serious	Not serious	Serious ^c	Not serious	25	23	study	Moderate
Uterine		-			-			-	,	1
perfor-			Not							
ation	1 ³	RCT	serious	Not serious	Serious ^c	Not serious	50	50	None reported	Moderate
Drotaverine										
		ic acia vs.	Piaceso							
Patient Pair										

							Number			
	Number						of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									Treatment group had	
									lower mean±SD pain	
Pain									scores vs. placebo	
during									group (2.32±1.137 vs.	
IUD place-	4.1	5.07	a . d					0.5	4.32±1.676,	
ment	14	RCT	Serious ^d	Not serious	Serious ^e	Not serious	31	25	p=0.001)*	Low
Highest										
level of pain after										
IUD place-									Treatment group had	
ment and									lower mean±SD pain	
before									scores vs. placebo	
clinic									group (1.28±0.59 vs.	
discharge	14	RCT	Serious ^d	Not serious	Serious ^e	Not serious	31	25	2.01±0.93, p=0.001)	Low
Placement S				1			<u> </u>			
									No difference (all	
									participants had	
Place-									successful	
ment									placements in both	
success	14	RCT	Serious ^d	Not serious	Serious ^e	Not serious	31	25	groups)	Low
Isonicotinic	acid hydra	zide (INH)	vs. placebo	0						
Patient Pain	<u> </u>									
Pain									Lower median pain	
during									VAS scores in	
tenac-									treatment groups vs.	
ulum									placebo groups (2 vs.	
place-			Not						4 cm, p<0.01; 3 vs. 5	
ment	2 ^{a,5,6}	RCT	serious	Not serious	Not serious	Not serious	210	210	cm, p=0.0001)*	High
									Lower mean pain	
Pain									VAS scores in	
during									treatment groups vs.	
IUD place-	225.6	5.07	Not .	l	l.,			242	placebo groups (3.9	
ment	2 ^{a,5,6}	RCT	serious	Not serious	Not serious	Not serious	210	210	vs. 5.3 cm, p<0.01;	High

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
					_			_	3.97 vs. 6.42 cm,	
									p=0.0001)*	
Highest level of										
pain after									Lower median pain	
IUD place-									VAS scores in	
ment and									treatment groups vs.	
before									placebo groups (2 vs.	
clinic			Not						3 cm, p<0.01; 2 vs. 4	
discharge	2 ^{a,5,6}	RCT	serious	Not serious	Not serious	Not serious	210	210	cm, p=0.0001)*	High
Provider Eas	se of Place	ment								
									Lower median ease	
									of insertion	
									(indicating easier	
									insertions) VAS	
									scores in treatment	
									groups vs. placebo	
Easy									groups (3 vs. 5 cm,	
place-			Not						p<0.01; 3 vs. 6 cm,	
ment	2 ^{a,5,6}	RCT	serious	Not serious	Not serious	Not serious	210	210	p=0.0001)*	High
Need for Ad	liunctive Pl	acement	Measures							
	•								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	
Cervical			Not						required dilation vs.	
dilation	2 ^{a,5,6}	RCT	serious	Very serious ^f	Not serious	Not serious	210	210	placebo group in	Low

							Number			
	Number						of	Number of		
_	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									second study (7.3%	
									vs. 16.5%, p=0.01)	
									Fewer participants in	
									treatment groups	
									requested analgesia	
									vs. placebo groups	
									(4.5% vs. 24.5%; 7%	
			Not						vs. 25%, p-values not	
Analgesia	2 ^{a,5,6}	RCT	serious	Not serious	Not serious	Not serious	210	210	reported)	High
Placement S	Success									
									First study: no	
									difference (all	
									participants had	
									successful	
									placements); Second	
									study: 2 failed	
									placements in	
									treatment group and	
Place-									4 failed placements	
ment	- 2.5.6		Not .	h					in placebo group	
success	2 ^{a,5, 6}	RCT	serious	Serious ^b	Not serious	Not serious	210	210	(p=0.594)	Moderate
Patient Satis	sfaction wi	th Proced	ure	I		I			T .	1
									Higher mean	
									satisfaction VAS	
									scores in treatment	
									groups vs. placebo	
									groups (8.1±0.6 vs.	
Patient									5.5±0.7, p<0.01; data	
satis-	2356	D.C=	Not	l		.	24.5	242	not reported,	10.1
faction	2 ^{a,5, 6}	RCT	serious	Not serious	Not serious	Not serious	210	210	p=0.0001)	High
Side Effects										

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

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

Footnotes

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^{*}Effect was statistically significant and clinically relevant.

^aEffect includes separate results from multiple studies examining the same outcome.

^bInconsistency is considered serious due to varying results among studies.

^cImprecision is considered serious due to the small number of events.

^dRisk of bias is considered serious due to the lack of information regarding allocation concealment.

^eImprecision is considered serious due to the small sample size.

finconsistency 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.

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

	Number of	Study	2.1 (2.				Number of patients:	Number of patients:				
Outcome	studies	design	Risk of Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty		
Vaginal dinor	rostone vs.	placebo										
Patient Pain												
Pain during tenaculum									SMD (95% CI): - 0.79 (-1.43, -			
placement	3 ¹⁻³	RCT	Not serious	Not serious	Not serious	Not serious	188	188	0.16)*	High		
Pain during uterine	-1.3								SMD (95% CI): - 0.88 (-1.54, -			
sounding	3 ¹⁻³	RCT	Not serious	Not serious	Not serious	Not serious	188	188	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	J						333		SMD (95% CI): -			
after IUD insertion	4 ¹⁻⁴	RCT	Not serious	Not serious	Not serious	Not serious	288	288	0.57 (-1.19, 0.05)	High		
	Insertion 4 ¹⁻⁴ RCT Not serious Not serious Not serious Not serious 288 0.05) High Provider Ease of Placement											

	Number of	Study					Number of patients:	Number of patients:			
Outcome	studies	design	Risk of Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty	
		J		,				•	SMD (95% CI): -	,	
Ease of									1.17 (-1.62, -		
insertion	5 ¹⁻⁵	RCT	Not serious	Not serious	Not serious	Not serious	388	388	0.73)*	High	
Need for Adj	Need for Adjunctive Placement Measures										
_									RR (95% CI):		
									0.34 (0.22,		
Analgesia	4 ¹⁻⁴	RCT	Not serious	Not serious	Not serious	Not serious	288	288	0.53)*	High	
Side Effects											
									RR (95% CI):		
					Very				3.73 (1.47,		
Fever	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	9.44)*	Low	
									RR (95% CI):		
					Very				1.03 (0.69,		
Nausea	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	1.53)	Low	
									RR (95% CI):		
					Very				2.11 (0.97,		
Vomiting	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	4.61)	Low	
									RR (95% CI):		
					Very				2.78 (0.95,		
Diarrhea	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	8.09)	Low	
									RR (95% CI):		
	-1.5				Very				2.38 (0.96,		
Shivering	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	5.90)	Low	
					1.,				RR (95% CI):		
Abdominal	_1 5				Very				1.76 (0.73,		
cramping	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	4.26)	Low	
Post-					Vam.				RR (95% CI):		
procedural	3 ^{1, 4, 5}	DCT	Not corio	Not corious	Very	Not sorious	280	200	1.02 (0.92,	Low	
bleeding		RCT	Not serious	Not serious	serious ^a	Not serious	280	280	1.14)	Low	
Adverse Ever	nts 	l			1/2				I		
Vasovagal	5 ¹⁻⁵	DCT	Not corio	Not corious	Very	Not sorious	200	200	None reported	Vondlow	
reaction	513	RCT	Not serious	Not serious	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					Very					
perforation	5 ¹⁻⁵	RCT	Not serious	Not serious	serious ^a	Not serious	388	388	None reported	Very Low
Patient Satisf	Patient Satisfaction with Procedure									
									SMD (95% CI):	
Patient									1.41 (0.62,	
satisfaction	4 ¹⁻⁴	RCT	Not serious	Not serious	Not serious	Not serious	288	288	2.20)*	High

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

Footnotes

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^{*}Statistically significant.

^aImprecision is considered very serious due to the rarity of events.

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 Tranex	Oral Tranexamic Acid vs. placebo									
Reduction of median number of bleeding/ spotting days	11	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 pvalue])	High
Adverse			Not							
events	1 ¹	RCT	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/									of	
spotting									bleeding/spotting	
days									days (Mefanamic	
									acid group: 29	
									[range of 15-44]	
									vs. placebo group:	
									33 [15-53.5]	
									[unknown p- value])	
Adverse	.1		Not							
events	1 ¹	RCT	serious	Not serious	Not serious	Not serious	63	61	None	High
UPA vs. pla	cebo		1	T		ı			1	
									No significant	
									reduction of	
Reduction									bleeding/spotting	
of									days (UPA group:	
bleeding/									13.5 vs. placebo	
spotting									group: 16.5 [p-	
days	1 ²	RCT	Serious ^c	Not serious	Not serious	Not serious	15	10	value= 0.49])	Moderate
Adverse events	1 ²	RCT	Serious ^c	Not sorious	Not serious	Not sorious	15	10	None	Moderate
		_	Serious	Not serious	Not serious	Not serious	13	10	None	Moderate
Oral Estrad	iol vs. place	bo	1			T			S: :5: .	T
									Significant	
5 1									reduction in	
Reduction		Non-							number of	
of		compar	Very						bleeding days	
bleeding	43	ative	serious ^{d,}		c . d		40	21/2	(Before: 68% vs.],, ,
days	1 ³	cohort	1,5	Not serious	Serious ^d	Not serious	19	N/A	After: 32%)	Very low
		Non-	1/2.55							
		compar	Very							
Adverse	43	ative	serious ^{d,}	Nist so:	Carrian d	Nick co. :	40	N1 / A	Name	1
events	1 ³	cohort	1,8	Not serious	Serious ^d	Not serious	19	N/A	None	Very low

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

Footnotes

^aRisk of bias is considered serious due to lack of blinding and placebo control for one arm of the trial.

^bRisk of bias is considered very serious due to differing group sizes with no explanation.

^cRisk of bias is considered serious or very serious due to high loss to follow-up.

^dImprecision is considered very serious due to small sample size.

^eRisk of bias is considered very serious due to lack of power calculations.

fRisk of bias is considered very serious due to lack of comparison with an age-matched group.

^gRisk of bias is considered very serious due to uncertain risk of confounding.

- 1. Sørdal T, Inki P, Draeby J, O'Flynn M, Schmelter T. Management of initial bleeding or spotting after levonorgestrel-releasing intrauterine system placement: a randomized controlled trial. Obstet Gynecol 2013;121:934-41. https://doi.org/10.1097/AOG.0b013e31828c65d8
- 2. Warner P, Guttinger A, Glasier AF, Lee RJ, Nickerson S, Brenner RM, Critchley HO. Randomized placebo-controlled trial of CDB-2914 in new users of a levonorgestrel-releasing intrauterine system shows only short-lived amelioration of unscheduled bleeding. Hum Reprod 2010;25:345-53. https://doi.org/10.1093/humrep/dep377
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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	High
	No trials investigated aspirin among ENG implant users.	
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	Moderate to High
	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}	
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}	Low to Moderate
	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. 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,	
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; 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. 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 (20	00mg) vs. pla	acebo - LN	ıG							
Percentage who stopped bleeding within 7									70% of celecoxib	
days of initiating treatment	1 ⁹	RCT	Not serious	Not serious	Not serious	Not serious	20	20	group vs. 0% of placebo group (p<0.0001)	High
Bleeding/s potting days in 28 days after initiating	10		Not						Mean (SD) days: 5.0±1.65 for celecoxib group vs. 19.0±6.50 for placebo group	
Duration of bleed-free	19	RCT	serious Not	Not serious	Not serious	Not serious	20	20	(p<0.001) Mean (SD) days: 24.0±1.65 for	High
interval in	1 9	RCT	serious	Not serious	Not serious	Not serious	20	20	celecoxib group vs.	High

Outcome s 28 days after initiating treatment	of studies	Study design	Risk of Bias	Inconsistency	Imprecision		patients:	patients:		
28 days after initiating	studies	design	Bias	Inconsistency	Imprecision					
after initiating						Indirectness	treatment	comparison	Effect	Certainty
initiating									10.0±6.50 for	
_									placebo group (p<0.001)	
treatment									(p<0.001)	
l									80% of celecoxib	
Satisfaction									group vs. 30% of	
with			Not						placebo group	
treatment	1 ⁹	RCT	serious	Not serious	Not serious	Not serious	20	20	satisfied (p<0.001)	High
Mefenamic acid		-			1100 30110 43	1100 30110 43	20		3dti3ffed (p 101001)	1
Percentage	u (Sooning i	טוט) vs. pi	acebo - Liv							<u> </u>
who										
stopped										
bleeding									26/34 (76%) of	
within 7									mefenamic acid	
days of									group vs. 9/33	
initiating			Not						(27%) of placebo	
treatment	1 ¹⁰	RCT	serious	Not serious	Not serious	Not serious	34	33	group (p<0.001)	High
Maintenan										
ce of										
bleeding-									23/34 (68%) of	
free									mefenamic acid	
interval 20									group vs. 11/33	
days or			Not						(33%) of placebo	
longer	1 ¹⁰	RCT	serious	Not serious	Not serious	Not serious	34	33	group (p<0.01)	High
Mean total										
number									Mean±SD days:	
bleeding/sp									11.6±8.2 for	
otting days									mefenamic acid	
within 28									group vs. 17.2±10.2 for	
days of treatment			Not						placebo group	
initiation	1 ¹⁰	RCT	serious	Not serious	Not serious	Not serious	34	33	(p<0.05)	High

	Number						Number of	Number of		
	of 	Study	Risk of				patients:	patients:	F.C	
Outcome Proportion	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
who										
stopped										
bleeding									15/23 (65.2%) of	
within 7									mefenamic acid	
days of									group vs. 5/23	
treatment			Not						(21.7%) of placebo	
initiation	1^{11}	RCT	serious	Not serious	Not serious	Not serious	23	23	group (p<0.05)	High
Proportion										
who										
stopped										
bleeding										
for > 20									13/23 (56.5%) of	
days within									mefenamic acid	
28 days of									group vs. 5/23	
treatment	. 11		Not						(21.7%) of placebo	
initiation	111	RCT	serious	Not serious	Not serious	Not serious	23	23	group (p<0.05)	High
T-4-1									Mean	
Total number of									bleeding/spotting	
bleeding/sp									days: 10.52 for mefenamic acid	
otting days									group vs. 16.78 for	
over 28			Not						placebo group	
days	1 ¹¹	RCT	serious	Not serious	Not serious	Not serious	23	23	(p<0.05)	High
,				g desogestrel + 2		1100 5011005			[(β 10.03)	1
Percent										
who										
stopped									32/42 (76%) of	
bleeding									COC group vs.	
within 7			Very						15/42 (35.7%) of	
days of			serious ^{a,}						mefenamic acid	
treatment	1 ¹²	RCT	b	Not serious	Not serious	Not serious	42	42	group (p<0.05)	Very Low

	Namelana						Number of	Neverland		
	Number of	Study	Risk of				patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Recurrence				Í				•		
of bleeding										
after									6 (14.3%) of COC	
stopping			Very						group vs. 3 (7.1%)	
treatment			serious ^{a,}						of mefenamic acid	
for >7 days	1 ¹²	RCT	b	Not serious	Not serious	Not serious	42	42	group (p=0.919)	Very Low
									Mean±SD days:	
Duration of									7.29±3.16 for COC	
bleeding									group vs.	
within 90			Very						10.57±4.14 for	
days of			serious ^{a,}						mefenamic acid	
treatment	1 ¹²	RCT	b	Not serious	Not serious	Not serious	42	42	group (p<0.05)	Very Low
Ibuprofen (80	00mg TID) v	s. placebo	- LNG							
Mean										
number of										
bleeding/sp										
otting days									Mean days: 0.75	
in 5 days									for ibuprofen	
after									group vs. 1.16 for	
initiating									placebo group (p-	
treatment	1 ¹³	RCT	Serious ^c	Not serious	Serious ^d	Not serious	42	44	value NS)	Low
Mean										
number of										
bleeding/sp										
otting days									Mean days: 1.76	
in 10 days									for ibuprofen	
after									group vs. 2.17 for	
initiating									placebo group (p-	
treatment	1 ¹³	RCT	Serious ^c	Not serious	Serious ^d	Not serious	42	44	value NS)	Low
Bleeding/s									Mean (SD) days:	
potting									6.2 (2.55) for	
days in 30									ibuprofen group	
days after	1 ¹³	RCT	Serious ^c	Not serious	Serious ^d	Not serious	42	44	vs. 6.4 (2.30) for	Low

	Number of	Charles	Risk of				Number of	Number of		
Outcome	studies	Study design	Bias	Inconsistency	Imprecision	Indirectness	patients: treatment	patients: comparison	Effect	Certainty
initiating	Studies	uesigii	Dias	inconsistency	IIIIprecision	manectness	treatment	companison	placebo group (p-	Certainty
treatment									value NS)	
Bleeding/s										
potting										
days in										
days 1-5									Mean days: 2.9 for	
after									ibuprofen group	
initiating	4.2	NDT					24	24	vs. 3.6 for placebo	.,
treatment	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	21	21	group (p-value NS)	Very Low
Bleeding/s potting									Mean days: 5.9 for	
days in									ibuprofen group	
days 1-20									vs. 11.1 for	
after									placebo group	
initiating									(significant, p-	
treatment	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	21	21	value NR)	Very Low
Total										
bleeding/sp										
otting days										
over 365-										
day follow-									Mean days: 94 for	
up (manulation) o									ibuprofen group	
(multiple courses									vs. 129 for placebo group (significant,	
allowed)	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	21	21	p-value NR)	Very Low
Aspirin (80m			Scrious	1401 3011003	1400 3011003	1400 3011003		21	p value (VIII)	very Low
Consecutiv	g, vs. placer	DO - LING							Median days: 6 for	
e									aspirin group, 7 for	
bleeding/sp									Vitamin E group, 7	
otting days									for vitamin E +	
after									aspirin group, 7 for	
initiating			Not						placebo group	
treatment	1 ¹	RCT	serious	Not serious	Not serious	Not serious	117	116	(p=0.19)	High

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	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	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			Not	Not serious	NOT SELIOUS	NOT SELIOUS			Mean days: 15.4 for tranexamic acid group vs. 12.7 for placebo group	
treatment	114	RCT	serious	Not serious	Not serious	Not serious	34	34	(p=0.182)	High
Hormonal Tr										
COC (150 mg	LNG + 30 με	g EE) vs. pl	lacebo - EN	l G			l			
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

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

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	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 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.	
Tatal			Mami						28.6±5.4 90 days	
Total bleeding/sp			Very serious ^{g,}						post-treatment	
otting days	1^{17}	RCT	h	Not serious	Not serious	Serious ⁱ	16	14	(NS); no direct comparison	Very Low
otting days	1	KCI		Not serious	Not serious	Serious	10	14	Total days: COC:	very Low
									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	
Number of									12.4±5.8 90 days	
bleeding/sp			Very						post-treatment	
otting days			serious ^{g,}						(NS); no direct	
per episode	1 ¹⁷	RCT	h	Not serious	Not serious	Serious ⁱ	16	14	comparison	Very Low
Reduction	-			.100 3011003		2011043		<u> </u>	COC group not	30.7 2000
in number			Very						significantly	
of			serious ^{g,}						decreased; Placebo	
bleeding/sp	1 ¹⁷	RCT	h	Not serious	Not serious	Serious ⁱ	18	14	not significantly	Very Low

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

Outcome stud days of treatment	dies design	Bias	Inconsistency	Imprecision		patients:	patients:		
•				iniprecision	Indirectness	treatment	comparison	Effect	Certainty
1									
Recurrence of bleeding after stopping treatment	12	Very serious ^{a,}						6 (14.3%) of COC group vs. 3 (7.1%) of mefenamic acid	
for ≥ 7 days 1^1	.12 RCT	D	Not serious	Not serious	Not serious	42	42	group (p=0.919)	Low
Duration of bleeding within 90 days of		Very serious ^{a,}						Mean±SD days: 7.29±3.16 for COC group vs. 10.57±4.14 for mefenamic acid	
treatment 1 ¹	.12 RCT	b	Not serious	Not serious	Not serious	42	42	group (p<0.05)	Low
EE (50 mcg) vs. plac	cebo - LNG								
Percentage who stopped bleeding within 3									
days of initiating	18 RCT	Serious ^a	Not corious	Not serious	Not serious	43	46	67% of EE group vs. 15% of placebo	Moderate
Bleeding/s potting days over 20 days of		Serious ^a	Not serious	NOT SETIOUS	NOT SELIOUS			group (p<0.0005) Mean (SD) days: 5.4 (5.1) days for EE group vs. 12.3 (5.4) days for placebo group	
treatment 1 ¹	.18 RCT	,j,n	Not serious	Not serious	Not serious	43	46	(p<0.00001)	Moderate
Percentage with bleeding- free 11	.18 RCT	Serious ^a	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/s potting days	1 ¹⁷	RCT	Very serious ^{g,}	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 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	Very Low
Number of bleeding/sp otting days per episode	1 ¹⁷	RCT	Very serious ^{g,}	Not serious	Not serious	Serious ⁱ	18	14	pre-treatment vs 12.4±5.8 90 days post-treatment (NS), no direct comparison	Very Low

	Number		511.6				Number of	Number of		
0	of	Study	Risk of Bias	In a su si at a u su .	luana na atata na	la dina ata a a a	patients:	patients:	Effe et	Cautaintu
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect EE: 3.4+0.4 90 days	Certainty
									pre-treatment vs. 3.0+0.2 90 days	
									l	
									post-treatment (NS); Placebo:	
									` "	
									3.4+0.4 90 days	
									pre-treatment vs.	
F			.,						3.5+0.5 90 days	
Episodes of			Very						post-treatment	
bleeding/sp	4 17		serious ^{g,}				4.0		(NS); no direct	l., .
otting	1 ¹⁷	RCT	"	Not serious	Not serious	Serious ⁱ	18	14	comparison	Very Low
									EE significantly	
									decreased (p<0.02,	
Reduction									no values	
in number									reported); Placebo	
of									not significantly	
bleeding/sp									decreased (no	
otting days			Very						values reported);	
during	. 17		serious ^{g,}						no direct	
treatment	117	RCT	n	Not serious	Not serious	Serious ⁱ	18	14	comparison	Very Low
Bleeding/s										
potting									_	
days in 20									4.5 for EE group vs.	
days after									11.1 for placebo	
initiating									group (significant,	
treatment	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	17	21	p-value NR)	Low
Total										
bleeding/sp										
otting days										
over 365-									77 for EE group vs.	
day follow-									129 for placebo	
up									group (significant,	
(multiple	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	17	21	p-value NR)	Low

	Number		211.6				Number of	Number of		
Outcome	of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	patients: treatment	patients: comparison	Effect	Certainty
courses allowed)	Staales	ucoigii	Diag	meensistemey	mprediction	muncomess	u cument	Companison	2.700	Cortainty
EE (20mcg) v	s. placebo -	LNG								
Mean										
number of										
bleeding/sp										
otting days									Mean days: 2.35	
in 10 days after			Very						for EE group vs.	
initiating			serious ^{c,}						2.17 for place	
treatment	1 ¹³	RCT	k	Not serious	Serious ^d	Not serious	20	44	group (p-value NS)	Very Low
Bleeding/s	_								В сар (р такаста)	,
potting									Mean (SD) days:	
days in 30									6.1 (2.63) for EE	
days after			Very						group vs. 6.4 (2.30)	
initiating	40		serious ^{c,}						for placebo group	
treatment	1 ¹³	RCT	k	Not serious	Serious ^d	Not serious	20	44	(p-value NS)	Very Low
Estradiol (100	Omcg) patch	vs. place	bo - LNG						T	
Proportion										
who showed										
clinical										
improveme										
nt										
(bleeding										
<8 days									23/33 in estraderm	
and/or									patch group vs.	
interval									13/31 in placebo	
>20 days)	1 ¹⁹	RCT	Serious ^j	Not serious	Very serious ^l	Not serious	33	31	group (p-value NR)	Very Low
LNG (30 mcg	BID) vs. pla	cebo - LNC	3							
Bleeding/s									8.9 for LNG group	
potting	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	21	21	vs. 11.1 for	Low

	Normalisa						Number of	Neverland		
	Number of	Study	Risk of				patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
days in 20		0		,	,				placebo group of	,
days after									days 1-20 after	
initiating									initiating	
treatment									treatment (p-value	
									NS)	
Total										
bleeding/sp										
otting days									101 for LNG group	
over 365-									vs. 129 for placebo	
day follow-									group (significant,	
ир	1 ²	NRT	Serious ^e	Not serious	Not serious	Not serious	21	21	p-value NR)	Low
Mifepristone	(25mg BID)	+ EE (20 r	ncg) vs. pla	cebo - ENG						
									Mean days (95%	
									CI) days: 4.2 days	
									(3.5-5.2) for Mife +	
									EE vs 7.5 days (6.1-	
Bleeding/s									9.1) for placebo	
potting									(p<0.05) (Weisberg	
days after									2006); Mife+EE:	
initiating									4.0 days (3.5-4.6)	
treatment									vs Placebo: 6.4	
until									days (5.1-8.0)	
bleeding			Not						(p<0.001)	
stopped	2 ^{4, 5}	RCT	serious	Not serious	Not serious	Not serious	82	81	(Weisberg 2009)	High
									Mean (95% CI)	
									days: 11.2 (9.0-	
									13.9) for mife + EE	
Duration of									vs. 15.3 (12.4-	
bleed-free									19.1) for placebo	
interval									(p-value NS)	
after									(Weisberg 2006);	
initiating			Not						No significant	
treatment	2 ^{4, 5}	RCT	serious	Not serious	Serious ^d	Not serious	82	81	differences (values	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									NR) (Weisberg	
									2009)	
									Mean (95% CI): 4.0	
									(3.5-4.5) for mife	
									+EE vs. 4.1 (3.6-	
									4.7) for placebo (p-	
									value NS)	
Episodes of									(Weisberg 2006);	
bleeding/sp									No significant	
otting after									differences (values	
initiating			Not						NR) (Weisberg	
treatment	2 ^{4, 5}	RCT	serious	Not serious	Serious ^d	Not serious	82	81	2009)	Moderate
Doxycycline (100mg BID)	+ EE (20n	ncg) vs. pla	cebo - ENG						
Bleeding/s										
potting										
days after									Mean (95% CI)	
initiating									days: 6.4 (4.8-8.6)	
treatment									for doxycycline+EE	
until									group vs. 6.4 (5.1-	
bleeding	1 ⁵	DOT	Not		6 · d		25	27	8.0) for placebo	
stopped Duration of	I°	RCT	serious	Not serious	Serious ^d	Not serious	35	37	group (p=NS)	Moderate
bleed-free										
interval										
after									No significant	
initiating			Not						difference (values	
treatment	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate
Episodes of		-					-		,	
bleeding/sp										
otting after									No significant	
initiating			Not						difference (values	
treatment	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate

							Number			
	Number of	Study	Risk of				of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
SERM/SPRM					·			·		
SERM: Tamo		g BID) vs. p	olacebo - Li	NG						
Percentage	, ,	<u> </u>								
who										
stopped										
bleeding									41 (82%) of	
within 7									tamoxifen group	
days of									vs. 28 (56%) of	
initiating			Not						placebo group	
treatment	1 ²⁰	RCT	serious	Not serious	Not serious	Not serious	50	50	(p=0.005)	High
									Mean±SD days: 1st	
									month: 6.24±0.70	
									for Tamoxifen	
									group vs.	
									12.29±0.84 for	
Bleeding/s									placebo group	
potting									(p=0.0003); 2nd	
days after									month: 6.78±0.91	
initiating			Not						vs. 11.87±0.83	
treatment	1 ²⁰	RCT	serious	Not serious	Not serious	Not serious	50	50	(p=0.0008)	High
									Mean±SD days:	
Duration of									33.2±20.9 days for	
bleed-free									Tamoxifen group	
interval									vs. 15.7±12.9 days	
after	20		Not						for placebo group	
treatment	1 ²⁰	RCT	serious	Not serious	Not serious	Not serious	50	50	(p=0.0003)	High
									After 1st month:	
									85.7% for	
									tamoxifen group	
									vs. 34.7% for	
Satisfaction									placebo group	
with	4.20	DOT	Not				50	50	(p<0.0005); After	
treatment	1 ²⁰	RCT	serious	Not serious	Not serious	Not serious	50	50	2nd month: 75.5%	High

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

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Outcome	Studies	uesigii	Did5	inconsistency	Imprecision	munectness	treatment	Comparison	15.2 (95% CI: 2.8,	Certainty
									27.5) (p=0.02)	
									(Simmons);	
									Tamoxifen vs.	
									placebo: 9.8 more	
									days (95% CI 4.6-	
									15.0) (Edelman)	
									Mean satisfaction	
									VAS score: 70.3	
									mm for tamoxifen	
									group vs. 49.3 mm	
									for placebo group	
									(p= 0.02); Median	
Satisfaction									(range) satisfaction	
with									VAS score: 71 (8.5-	
bleeding									100) for tamoxifen	
pattern									group vs. 31 (0-	
after 1st			Not						100) for placebo	
treatment	2 ^{21, 22}	RCT	serious	Not serious	Not serious	Not serious	76	73	group (p<0.001)	High
Satisfaction									Median (range)	
with									satisfaction VAS	
bleeding									score: 62 (16-100)	
pattern									tamoxifen vs. 46	
after 90			Not						(0-100) placebo	
days	1 ²²	RCT	serious	Not serious	Not serious	Not serious	45	44	(p=0.023)	High
									Mean±SD	
									satisfaction VAS	
Satisfaction									score: 61.4±24.7	
with									for tamoxifen	
bleeding									group vs.	
pattern									53.6±33.3 for	
after 180	24								placebo group	
days	1 ²¹	RCT	Serious ^c	Not serious	Not serious	Not serious	22	21	(p=0.39)	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
SPRM: Mifep	ristone (50r	ng) vs. pla	cebo - LNG							
									Mean days: Mife:	
									48 <u>+</u> 15 in 1st 90d	
Bleeding/s									reference period	
potting									(no treatment) vs.	
days in 90									29 in 2nd 90d	
day									reference period	
reference									(p<0.0002);	
period									Placebo: 51 <u>+</u> 15 in	
after									1st 90d reference	
initiating									period (no	
treatment									treatment) vs. 33	
(includes 4									in 2nd 90d	
monthly									reference period	
treatments	. 2		Not						(p<0.0002), no	
)	1 ³	RCT	serious	Not serious	Not serious	Serious ⁱ	50	50	direct comparison	Moderate
									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	
Dstism of									90d reference	
Duration of									period (no	
bleeding									treatment) vs. 11.1	
episodes after									days n 2nd 90d	
initiating			Not						reference period (p=0.0003); no	
	1 ³	DCT		Not sorious	Not serious	Sorious ⁱ	50	E0.		Moderate
treatment	1-	RCT	serious	Not serious	Not serious	Serious ⁱ	50	50	direct comparison	Moderate

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
									37% for	
Satisfaction									mifepristone group	
with	2		Not						vs. 18% for placebo	_
treatment	1 ³	RCT	serious	Not serious	Not serious	Serious ⁱ	48	49	group (p<0.01)	Moderate
SPRM: Mifep	ristone (25r	ng BID) vs	. placebo -	ENG	l					
Bleeding/s										
potting										
days after									Mean (95% CI)	
initiating									days: 5.9 (4.8-7.2)	
treatment									for mifepristone	
until									group vs. 7.5 (6.1-	
bleeding			Not						9.1) for placebo	_
stopped	14	RCT	serious	Not serious	Not serious	Not serious	42	44	group (p=0.283)	High
									Mean (95% CI)	
Duration of									days: 10.4 (8.3-	
bleed-free									13.0) for	
interval									mifepristone vs.	
after									15.3 (12.4-19.1) for	
initiating			Not						placebo (p-value	
treatment	14	RCT	serious	Not serious	Not serious	Not serious	42	44	NS)	High
									Mean (95% CI)	
Episodes of									days: 4.7 (4.1-5.3)	
bleeding/sp									for mifepristone	
otting after									group vs. 4.1 (3.6-	
initiating			Not						4.7) for placebo	
treatment	14	RCT	serious	Not serious	Not serious	Not serious	42	44	group (p-value NS)	High
SPRM: Mifep	ristone (25r	ng BID) +	EE (20 mcg)	vs. placebo - EN	iG					
Bleeding/s									Mean days (95%	
potting									CI) days: 4.2 days	
days after									(3.5-5.2) for Mife +	
initiating									EE vs 7.5 days (6.1-	
treatment			Not						9.1) for placebo	
until	2 ^{4, 5}	RCT	serious	Not serious	Not serious	Not serious	82	81	(p<0.05); Mife+EE:	High

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
bleeding									4.0 days (3.5-4.6)	
stopped									vs placebo: 6.4	
									days (5.1-8.0)	
									(p<0.001)	
									Mean (95% CI)	
Duration of									days: 11.2 (9.0-	
bleed-free									13.9) for mife + EE	
interval									vs. 15.3 (12.4-	
after									19.1) for placebo	
initiating			Not						(p-value NS)	
treatment	2 ^{4, 5}	RCT	serious	Not serious	Serious ^d	Not serious	82	81	(Weisberg 2006)	Moderate
									Mean (95% CI): 4.0	
									(3.5-4.5) for mife	
									+EE vs. 4.1 (3.6-	
Episodes of									4.7) for placebo (p-	
bleeding/sp									value NS)	
otting after									(Weisberg 2006);	
initiating			Not						No significant	
treatment	2 ^{4, 5}	RCT	serious	Not serious	Serious ^d	Not serious	82	81	difference	Moderate
SPRM: Mifep	ristone (25r	ng) + Dox	ycycline (10	00mg BID) vs. pla	cebo - ENG					
Bleeding/s									Mean (95% CI)	
potting									days: 4.4 (3.8-5.2)	
days after									for	
initiating									doxycycline+mifep	
treatment									ristone group vs.	
until									6.4 (5.1-8.0) for	
bleeding			Not						placebo group	
stopped	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	(p=0.0108)	Moderate
Duration of										
bleed-free									No significant	
interval			Not						difference (values	
after	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	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/sp otting after initiating			Not						No significant difference (values	
treatment	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate
SPRM: UPA (15 mg) vs. p	lacebo - E	NG							
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. place	bo -ENG							

	Number						Number of	Number of		
	of	Study	Risk of				patients:	patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
				_				•	Mean (95% CI)	_
									days: 4.8 (3.9-5.8)	
									for doxy vs. 7.5	
									(6.1-9.1) for	
									placebo (p<0.05)	
Bleeding/s									(Weisberg 2006);	
potting									6.4 (4.4-9.2) for	
days after									doxy vs. 6.4 (5.1-	
initiating									8.0) for placebo,	
treatment									no significant	
until									differences (values	
bleeding			Not						NR) (Weisberg	
stopped	2 ^{4, 5}	RCT	serious	Serious ^m	Serious ^d	Not serious	75	81	2009)	Low
									Mean (95% CI)	
									days: 12.4 (9.9-	
									15.4) for doxy vs.	
									15.3 (12.4-19.1) for	
									placebo (p-value	
Duration of									NS) (Weisberg	
bleed-free									2006); No	
interval									significant	
after									differences (values	
initiating	-45		Not		.				NR) (Weisberg	
treatment	2 ^{4, 5}	RCT	serious	Not serious	Serious ^d	Not serious	75	81	2009)	Moderate
									Mean (95% CI): 4.6	
									(4.0-5.2) for doxy	
									vs. 4.1 (3.6-4.7) for	
									placebo (p-value	
Enicodes of									NS) (Weisberg	
Episodes of									2006); No	
bleeding/sp									significant	
otting after			Not						differences (values	
initiating	2 ^{4, 5}	DCT	Not	Not sorious	Coriousd	Not sorious	75	01	NR) (Weisberg	Moderate
treatment	۷"۶	RCT	serious	Not serious	Serious ^d	Not serious	75	81	2009)	Moderate

							Number					
	Number						of	Number of				
	of	Study	Risk of				patients:	patients:				
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty		
Doxycycline	Doxycycline (100mg BID) + EE (20mcg) vs. placebo - ENG											
Bleeding/s												
potting												
days after									Mean (95% CI)			
initiating									days: 6.4 (4.8-8.6)			
treatment									for doxycycline+EE			
until									group vs. 6.4 (5.1-			
bleeding			Not						8.0) for placebo			
stopped	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	group (p=NS)	Moderate		
Duration of												
bleed-free												
interval												
after									No significant			
initiating	_		Not						difference (values			
treatment	15	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate		
Episodes of												
bleeding/sp												
otting after									No significant			
initiating			Not						difference (values			
treatment	1 ⁵	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate		
	(25mg) + D	oxycycline	e (100mg B	ID) vs. placebo -	ENG	T	T					
Bleeding/s									Mean (95% CI)			
potting									days: 4.4 (3.8-5.2)			
days after									for			
initiating									doxycycline+mifep			
treatment									ristone group vs.			
until									6.4 (5.1-8.0) for			
bleeding	1 ⁵	DCT	Not	Nat assiste	Cariarrad	Nat assiste	25	27	placebo group	NA - do wat -		
stopped	l 1	RCT	serious	Not serious	Serious ^d	Not serious	35	37	(p=0.0108)	Moderate		
Duration of bleed-free									No significant			
			Not						No significant			
interval	1 ⁵	DCT	Not	Not sorious	Serious ^d	Not serious	35	37	difference (values	Moderate		
after	1-	RCT	serious	Not serious	Serious"	Not serious	33	5/	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/sp otting after initiating			Not						No significant difference (values	
treatment	15	RCT	serious	Not serious	Serious ^d	Not serious	35	37	NR)	Moderate
Vitamin E										
Vitamin E (20	0mg) vs. pla	acebo - LN	IG				I			
Consecutiv e bleeding/sp otting days after initiating treatment Total bleeding/sp	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
otting 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			Not						Median days: 16 for Vit E group, 16 for Vit E+aspirin group, 15 for aspirin group, 15 for placebo group	
treatment	1 ¹	RCT	serious	Not serious	Not serious	Not serious	112	111	(p=0.96)	High

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
Consecutiv e bleeding/sp otting days after initiating treatment	11	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	11	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

^aRisk of bias is considered serious due to the difference in baseline characteristics between groups, which was not adjusted for in analyses.

fRisk 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.

^gRisk of bias is considered very serious due to the lack of explanation of the measurement of outcomes.

^bRisk of bias is considered serious due to the lack of blinding of study participants or staff.

^cRisk of bias is considered serious or very serious due to the high loss to follow-up.

^dImprecision is considered serious due to the insufficient sample size to meet power calculations.

^eRisk of bias is considered serious due to the lack of information on participation or compliance.

^hRisk of bias is considered very serious due to the lack of information on the drop-out rate.

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

^jRisk of bias is considered serious due to the lack of explanation of randomization and allocation processes.

^kRisk of bias is considered serious due to the differential compliance between groups with the study drug.

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

^mInconsistency is considered serious due to inconsistent results between two studies.

ⁿRisk 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.

Outcomo	Number of	Study	Risk of	Inconsistancy	Impresision	Indirectness	Number of patients:	Number of patients:	Effort	Cortainty
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
Initiation		_								
Effect of UPA or	n the effecti	iveness of	hormonal o	contraception to su	ippress ovulation	on	T		T	
Effectiveness	-1.3		Not						No significant difference	
(Ovulation)	21, 2	RCT	serious	Not serious	Not serious	Serious ^a	68	66	(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 hormo	nal contrac	eption on	the effectiv	eness of UPA to d	elay ovulation					
Effectiveness			Not		, , , , , , ,				Increased risk of ovulation with UPA+DSG vs UPA+PLB	
(Ovulation)	1 ²	RCT	serious	Not serious	Not serious	Serious ^a	29	29	(p=0.0244)	Moderate

	Number of	Study	Risk of				Number of patients:	Number of patients:		
Outcome	studies	design	Bias	Inconsistency	Imprecision	Indirectness	treatment	comparison	Effect	Certainty
		_							Increased risk of ovulation with UPA+COCs vs	
Effectiveness			Not						UPA alone	
(Ovulation)	1 ³	Cohort	serious	Not serious	Not serious	Serious ^a	33	33	(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			•						·	·
	nal contrac	eption on t	the effectiv	eness of UPA to de	lay ovulation					
Effectiveness (Ovulation [days 0-5])	14	RCT	Not serious	Not serious	Not serious	Serious ^a	50	50	No ovulations in either group	Moderate
Effect of UPA on	the effect	iveness of	hormonal c	ontraception to su	ppress ovulation	on				
Effectiveness (Ovulation			Not	·					Increased risk of ovulation with delayed COC start vs immediate COC start after	
[days 0-26])	14	RCT	serious	Not serious	Not serious	Serious ^a	50	50	UPA (p= 0.042)	Moderate

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

Footnotes

^aIndirectness is considered serious due to the use of ovulation as a proxy measure for the effectiveness of contraception to prevent pregnancy.

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^bImprecision is considered serious due to insufficient power to identify outcome.

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