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SYSTEMATIC REVIEW OPEN ACCESS

The Effectiveness of Non-Steroidal Anti-Inflammatory Drugs for Pain Relief During Outpatient Intrauterine Device Insertion: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Fear of procedural pain is a significant barrier to intrauterine device (IUD) uptake. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in IUD insertion for their analgesic and anti-inflammatory properties; however, evidence for their effectiveness remains inconsistent.

Aims: This systematic review and meta-analysis aimed to synthesise current evidence regarding the effectiveness of NSAIDs for pain relief during outpatient IUD insertion.

Materials and Methods: A search of MEDLINE, Embase, Cochrane Central Register of Controlled Trials, CINAHL and Scopus was performed from inception to March 3, 2025. The search strategy was developed using the Population, Intervention, Comparator, Outcome (PICO) framework. Two reviewers independently selected studies, extracted data and assessed included studies for bias using the Risk of Bias 2 (RoB 2) tool. Trials comparing pain scores between NSAID and placebo were pooled in a meta-analysis.

Results: Twenty-two studies, published between 2006 and 2024, met inclusion criteria. Ibuprofen ($n = 6$) was most used, followed by diclofenac ($n = 4$) and naproxen ($n = 4$). NSAIDs were administered orally ($n = 17$), intramuscularly ($n = 2$) and rectally ($n = 2$), with route not specified in one study. A meta-analysis of fourteen studies comparing NSAID with placebo, with a total sample size of 3358, found a statistically significant reduction in pain scores (mean reduction 0.77, 95% CI −1.29, −0.25). Side effects and adverse events did not differ significantly between groups.

Conclusions: Our review demonstrates an analgesic role for NSAIDs during IUD insertion, with a significant reduction in pain scores when compared to placebo. This evidence, limited by clinical and statistical heterogeneity, is of low certainty.

1 | Introduction

1.1 | Rationale

As one of the most effective forms of long-acting reversible contraception (LARC), the intrauterine device (IUD) benefits both users and health systems [1, 2]. The easily reversible 'set and forget' IUD is suitable for women of all ages, including nulliparous women and offers many non-contraceptive benefits such as reduced menstrual bleeding and pelvic pain. It is also an option for hormonal contraception when oestrogen-containing contraceptives are contraindicated [3, 4]. From a health system level, LARCs can also bring benefits by reducing unplanned pregnancies and/or terminations [1].

Well-documented fears of pain with IUD insertion remain a significant barrier to IUD uptake [5, 6]. Poor insertion experiences may discourage future IUD use [7], thereby preventing patients from accessing the medical and psychosocial benefits of LARCs [1–4]. Despite a substantial body of research surrounding interventions to reduce insertion pain, there is no gold-standard recommendation for pain management [8–10]. Analgesia regimens may further vary by clinician preference and local protocols—highlighting the need for high-quality research to develop evidence-based recommendations for analgesia in IUD insertion.

The analgesic and anti-inflammatory effects of non-steroidal anti-inflammatory drugs (NSAIDs) mean they are widely used for pain management during IUD insertion, despite inconsistent evidence regarding their effectiveness. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists make no explicit mention of NSAIDs in practice guidelines, but do state that oral analgesia one hour prior to insertion 'may be helpful' [8]. In contrast, the American College of Obstetricians and Gynecologists acknowledge inconsistent findings of NSAID efficacy, but suggest their low risk profile and potential benefit in reducing post-procedural pain make NSAID use justifiable [9].

There have been several attempts to analyse the benefits of NSAID use for IUD insertion pain. A 2015 Cochrane systematic review included six studies examining oral NSAIDs and one examining intramuscular NSAIDs for pain relief during insertion; only two demonstrated significant between-group differences. The review concluded that there is limited and varied evidence of NSAID efficacy [11]. Most recently, a systematic review by Martingano et al. [12] concluded that prophylactic NSAIDs show limited efficacy in reducing insertion pain, whilst acknowledging a paucity of high-quality studies. A 2022 Cochrane systematic review protocol indicates new evidence synthesis is forthcoming, though it may be some time away [13].

This systematic review and meta-analysis aimed to synthesise available evidence regarding the efficacy of NSAIDs for pain relief during outpatient IUD insertion. We argue an updated systematic review and meta-analysis is warranted for several reasons:

- NSAIDs are accessible, low-cost medications that require little clinician expertise to administer (e.g., in comparison to a cervical block);
- Previous reviews of pain during IUD insertion have not systematically explored factors that may contribute to one's pain experience—for example, parity, age and IUD type; and
- Recent systematic reviews have lacked meta-analyses to enhance the statistical power of existing evidence.

1.2 | Objectives

The study's review question was developed in line with the Population, Intervention, Comparator, Outcome (PICO) framework [14]. The review's PICO framework (see Supporting Information) specified the following:

- Population—women undergoing outpatient IUD insertion;
- Intervention—pre-procedural NSAID administration;
- Comparator—placebo or an alternative analgesic;
- Outcomes—pain scores measured during the procedure and secondary clinical outcomes.

A systematic review of the literature was conducted according to the preferred reporting of items for systematic reviews and meta-analyses (PRISMA) guidelines [15]. The review's primary objective was to evaluate the efficacy of NSAIDs on reducing pain experienced by patients undergoing IUD insertion. Primary outcomes included pain intensity at time of IUD insertion measured on a visual analogue scale (VAS) or numerical rating scale (NRS). Secondary outcomes included pain at other procedural timepoints, need for additional analgesia and medication-related events.

Prior to commencement of the literature review, a protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on March 3, 2025, in accordance with PRISMA guidelines (CRD420251003261) [16].

2 | Methods

2.1 | Eligibility Criteria

Randomised controlled trials (RCTs) and non-randomised studies with appropriate controls examining the effect of a NSAID on pain experienced during IUD insertion were considered for inclusion. Observational studies, case reports and case series were excluded. There were no restrictions placed on setting, context, date of publication or language.

2.2 | Information Sources

The databases MEDLINE (via Ovid), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and Scopus were searched from inception until March 3, 2025. Databases with Medical Subject Headings (MeSH) indexing were searched with both MeSH and keyword terms. Detailed search strategies for all included databases are provided in Supporting Information. Backwards and forward citation searching of references cited in included articles was completed via Scopus on July 7, 2025.

2.3 | Selection Process

Title and abstract screening were undertaken by two reviewers (M.B. and J.A.), who independently screened articles for eligibility using pre-defined criteria. Disagreements were resolved by discussion with a third reviewer (N.D.). The Covidence platform [17] facilitated the review process and automatically removed duplicates. This was supplemented by

manual duplicate removal where required. Full-text screening followed the same process, with reasons for exclusion documented.

2.4 | Data Collection

Data was independently extracted by M.B. and J.A. using a predefined plan into an Excel spreadsheet. Disagreements were resolved by a third reviewer (N.D.). A web-based programme (WebPlotDigitiser, accessed via https://automeris.io) was used to estimate data from figures when tabulated data was not available. Corresponding authors were contacted by email twice within one month if eligible studies did not report data of interest.

2.5 | Data Extraction and Analysis

Variables for which data were sought included participant characteristics (mean age, parity), intervention details (drug, dose, route of administration, timing of dose) and procedural outcomes (pain at various timepoints including IUD insertion, need for additional analgesia and medication-related events).

Studies that reported pain scores (either VAS or NRS) as median and interquartile range were converted to mean and standard deviation (SD) using the method described by Wan et al. [18] If studies reported standard error of the mean (SEM), SD was calculated using the equation 'SD = SEM × sqrt (sample size)'. All pain measurements were standardised to a 10 cm scale.

Cohort parity was presented as the percentage of nulliparous patients to best reflect individual study reporting. Safety outcomes were defined as serious adverse events including vasovagal/syncopal episode, anaphylaxis or uterine perforation; all other reported medication effects were considered side effects.

2.6 | Risk of Bias Assessment

Risk of bias was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool for randomised trials, independently completed by two authors (M.B. and J.A.) [19]. The five domains of assessment included:

1. Bias arising from the randomisation process;
2. Bias due to deviations from intended interventions;
3. Bias due to missing outcome data;
4. Bias in measurement of the outcome; and
5. Bias in selection of the reported result.

Studies were considered at overall low risk of bias if they were judged to be at low risk of bias for all domains. Two or fewer domains with some concerns resulted in an overall judgement of some concerns for bias. Studies with more than two domains with some concerns of bias or a single domain at high risk of bias were deemed at a high risk of bias.

Any disagreements were resolved through discussion with a third author (ND). The RoB 2 tool provided an algorithmic judgement, which was paired with assessor judgements to determine the study's overall risk of bias. The *robvis* tool was used to present this data [20].

2.7 | Synthesis Methods

Since all studies measured absolute difference in pain score on the same scale, a meta-analysis of the weighted mean difference using random effects was performed, given expected study heterogeneity. Weights were assigned using the inverse variance method, with the heterogeneity estimate taken from the Restricted Maximum-Likelihood model. The continuous outcome of pain intensity, measured on a ten-point numerical scale, was presented as mean difference with 95% confidence intervals (calculated using the Wald-type method).

Between-study heterogeneity was quantified using the I^2 statistic. Statistical significance of the overall treatment effect was assessed using the Z-test, with p-values < 0.05 considered statistically significant.

Subgroup analyses were planned for NSAID type, dose, timing of administration, patient parity and IUD type. Meta-regression was used to explore sources of heterogeneity, using the specific effect estimate as the dependent variable and study variables as independent variables. Year of study publication was explored with cumulative meta-analysis. Sensitivity analysis using the STATA meta-influence command was performed to assess whether any meta-analysed studies significantly impacted overall results. Publication bias was assessed through visual inspection of funnel plots and Egger's test. All analyses were conducted using Cochrane Review Manager (RevMan) version 9.11.0 and replicated on STATA version 16.0 for verification.

2.8 | Certainty of Evidence Assessment

Certainty of evidence was assessed and presented using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which considered risk of bias, inconsistency, indirectness, imprecision and publication bias [21, 22].

3 | Results

3.1 | Search Results

The search strategy retrieved 2009 articles (as 2007 unique studies), of which 252 duplicates were removed. The remaining 1755 articles underwent title and abstract screening, with 36 full texts assessed for eligibility. Eleven studies were excluded as they did not meet inclusion criteria; the full texts of a further three studies were unable to be retrieved. Figure 1 demonstrates this information in line with PRISMA recommendations.

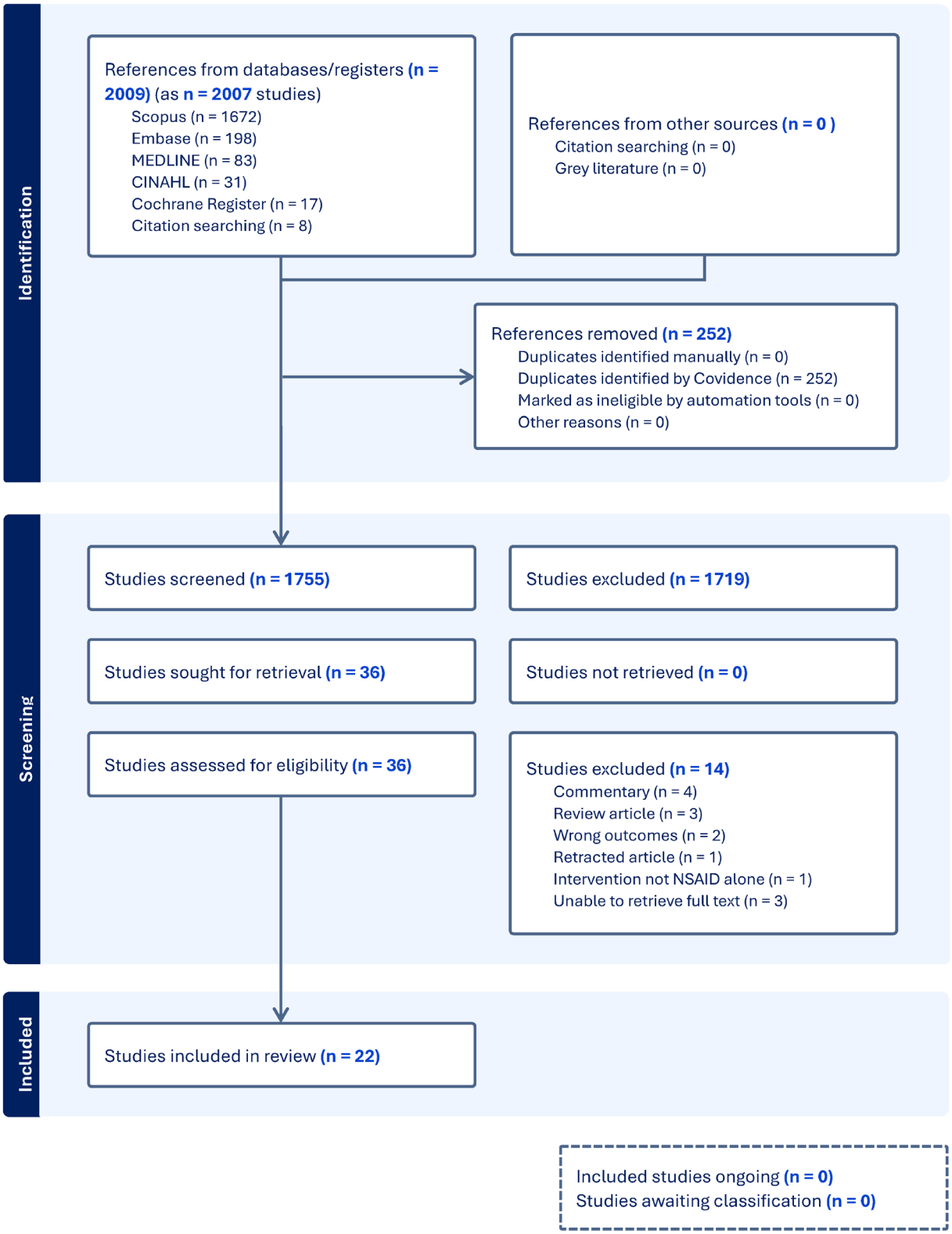

FIGURE 1 | PRISMA flow chart [17].

3.2 | Characteristics of Included Studies

A total of 22 studies met inclusion criteria, all of which were RCTs. Study characteristics are listed in Table 1. Included studies were published between 2006 and 2024. The most common countries of origin were Egypt ($n = 7$) [23–25, 27, 31, 33, 42], the United States ($n = 6$) [26, 29, 30, 37–39] and Brazil ($n = 4$) [28, 32, 36, 43]. Twelve studies placed copper IUDs only [23–25, 27, 31, 33–35, 40–42, 44], four placed hormonal (levonorgestrel-releasing) IUDs only [28, 29, 32, 43] and six studies placed both copper and hormonal IUDs [26, 30, 36–39]. IUDs were largely placed in the hospital setting ($n = 15$) [23–25, 27, 28, 30–33, 35,

TABLE 1 | Study characteristics and risk of bias assessment.

Source	Design	Sample size (*n*)	Study location	Setting	IUD type	Intervention age (mean [SD])	Intervention parity[a] (%)	Comparator age[b] (mean [SD])	Comparator parity[a,b] (%)	Intervention NSAID	NSAID route	NSAID dose (mg)	Primary outcome[d]	Risk of bias
Abbas et al., 2018 [23]	RCT	140	Egypt	Hospital	Copper	26.6 (4.6)	Not described	25.7 (3.9)	Not described	Ketoprofen	PO	150	Pain during insertion (VAS)	Some concerns
Abbas et al. 2018 [24]	RCT	107	Egypt	Hospital	Copper	30.7 (6.7)	Not described	29.9 (6.3)	Not described	Diclofenac	PO	50	Pain during insertion (VAS)	Some concerns
Abbas et al. 2017 [25]	RCT	94	Egypt	Hospital	Copper	29.1 (6.3)	Not described	28.5 (5.6)	Not described	Indomethacin	PR	50	Pain during insertion (VAS)	Some concerns
Bednarek et al., 2015 [26]	RCT	202	United States	Medical Centre	Both	28.8 (17.3)	36.6	29.5 (19.6)	35.6	Ibuprofen	PO	800	Pain during insertion (VAS)	Low
Beheiry et al., 2021 [27]	RCT	64	Egypt	Hospital	Copper	26.0 (6.4)	Not described	23.3 (5.5)	Not described	Diclofenac	IM	75	Pain during insertion, ease of insertion	Some concerns
Castro et al., 2014 [28]	RCT	98	Brazil	Hospital	LNG-IUS	30.6 (6.3)	43.7	30.4 (5.6)	44.0	Ibuprofen	PO	400	Pain during insertion (VAS)	Some concerns
Chor et al., 2012 [29]	RCT	81	United States	Medical Centre	LNG-IUS	24.7 (5.4)	6.8	27.9 (6.5)	0.0	Ibuprofen	PO	800	Pain during insertion (VAS)	Some concerns
Crawford et al., 2017 [30]	RCT	71	United States	Hospital	Both	31.9 (6.7)	2.9	30.7 (8.9)	13.9	Ketorolac	PO	20	Pain during insertion (NRS)	Some concerns
Darweesh et al., 2020 [31]	RCT	105	Egypt	Hospital	Copper	28.4 (6.5)	Not described	29.3 (7.1)	Not described	Celecoxib	PO	200	Pain during insertion (VAS)	Low
de Oliveira et al., 2021 [32]	RCT	100	Brazil	Hospital	LNG-IUS	22.2 (2.0)	83.7	22.2 (1.7)	88.2	Naproxen	PO	550	Pain during insertion (VAS)	Some concerns
Fahmy et al., 2016 [33]	RCT	150	Egypt	Hospital	Copper	27.4 (4.8)	Not described	28 (4.1)	Not described	Oral NSAIDs[c]	PO	Not described	Pain scores at multiple points of insertion procedure (VAS)	Some concerns
Hubacher et al., 2006 [34]	RCT	2018	Chile	Medical Centre	Copper	Not described	Not described	Not described	Not described	Ibuprofen	PO	400	Pain during insertion (VAS)	Low
Karabayirli et al., 2012 [35]	RCT	34	Türkiye	Hospital	Copper	35.0 (4)	Not described	36.5 (5.0)	Not Described	Naproxen	PO	550	Pain during insertion (VAS)	Some concerns
Marcelino et al., 2024 [36]	RCT	120	Brazil	Hospital	Both	Not described	Not described	Not described	Not described	Ketorolac	PO	20	Pain during insertion (VAS)	Low

(Continues)

TABLE 1 | (Continued)

Source	Design	Sample size (*n*)	Study location	Setting	IUD type	Intervention age (mean [SD])	Intervention parity[a] (%)	Comparator age[b] (mean [SD])	Comparator parity[a,b] (%)	Intervention NSAID	NSAID route	NSAID dose (mg)	Primary outcome[d]	Risk of bias
Miles et al., 2019 [37]	RCT	156	United States	Military Treatment Facility	Both	31.2 (6.5)	27.5	30.6 (7.6)	37.6	Naproxen	PO	375	Pain immediately after insertion (VAS)	Low
Ngo et al., 2015 [38]	RCT	67	United States	Women's Health Clinic	Both	26.6 (5.1)	24.2	27.3 (5.4)	23.5	Ketorolac	IM	30	Pain during insertion (VAS)	Low
Ngo et al., 2016 [39]	RCT	118	United States	Medical Centre	Both	23.2 (3.9)	98.3	24.3 (4.2)	96.7	Naproxen	PO	550	Pain during insertion (VAS)	Low
Peerananrangsee et al., 2018 [40]	RCT	130	Thailand	Hospital	Copper	34.6 (7.4)	0.0	36.1 (6.8)	0.0	Etoricoxib	PO	120	Pain during insertion (VAS)	Some concerns
Sääv et al., 2007 [41]	RCT	79	Sweden	Hospital	Copper	23.1 (2.9)	Not described	22.7 (3.1)	Not described	Diclofenac	Not described	100	Cervical resistance	Some concerns
Sakna et al., 2023 [42]	RCT	140	Egypt	Hospital	Copper	31.6 (4.4)	0.0	32.3 (3.7)	0.0	Ibuprofen	PO	400	Pain immediately after insertion (VAS)	High
Vitti et al., 2012 [43]	RCT	80	Brazil	Not described	LNG-IUS	Not described	Not described	Not described	Not described	Ibuprofen	PO	400	Pain during insertion (VAS and faces scale)	High
Yanney et al., 2023 [44]	RCT	99	Ghana	Hospital	Copper	Not described	Not described	Not described	Not described	Diclofenac	PR	100	Pain during and after insertion (VAS)	Some concerns

[a]Parity presented as proportion of nulliparous patients to best reflect variances in individual study reporting.
[b]For studies with more than one comparator, mean age and parity reflect entire comparator sample.
[c]Further detailed as 'such as naproxen'.
[d]Where VAS describes Visual Analogue Scale, and where NRS describes Numerical Rating Scale.

36, 40–42, 44], with the remaining in a medical centre ($n=4$) [26, 29, 34, 39], women's health clinic ($n=1$) [38] and military treatment facility ($n=1$) [37]. The setting of one study was not adequately described [43].

There was significant variation in the intervention NSAID, including in dose and route of administration (Table 1). Ibuprofen ($n=6$) [26, 28, 29, 34, 42, 43] was the most common NSAID studied, followed by diclofenac ($n=4$) [23, 27, 41, 44] and naproxen ($n=4$) [32, 35, 37, 39]. Most commonly, NSAIDs were given orally (PO; $n=17$) [23, 24, 26, 28–37, 39, 40, 42, 43]; they were also administered intramuscularly (IM; $n=2$) [27, 38] and rectally (PR; $n=2$) [25, 44]. One study did not describe route of administration [41]. Comparator medications also varied—fifteen studies compared an NSAID with placebo [24–27, 29–31, 33–40], five with a cervical block (four with 2% lidocaine [28, 32, 37, 43] and one with 1% lidocaine) [31] and two with a 10% lidocaine cervical spray [42, 44]. Other comparators included misoprostol ($n=2$) [27, 41], tramadol ($n=1$) [35] and hyoscine butyl-bromide ($n=2$) [23, 31].

All included trials described an appropriate randomisation strategy, mostly using computer-randomisation. Similarly, most studies reported appropriate allocation concealment, either with envelopes or pharmacy packages. Sixteen studies were double-blinded [23–27, 29–31, 33–40], one single-blinded [41], three non-blinded [28, 32, 41] and two not adequately described [42, 43].

3.3 | Risk of Bias Assessment

Study risk of bias is displayed in Table 1, with detailed assessment in Appendix A. Two studies were deemed at high risk of bias. One, a conference abstract, was considered at high risk of bias due to limited information on the study's design [43]. The other's blinding status was unknown, and it was unclear if participants and/or investigators were aware of participants' assigned interventions [42].

Visual inspection of a funnel plot showed no evidence of publication bias. Egger's test showed no evidence of small study effects ($p=0.454$).

3.4 | Results of Individual Studies

Six studies reported a significant reduction in pain scores with an NSAID at the time of IUD insertion [24, 25, 30, 31, 35, 44]. Four compared their chosen NSAID with placebo [24, 25, 30]. Darweesh et al. [31] compared celecoxib with hyoscine butyl-bromide and placebo, finding a statistically significant reduction in pain during IUD insertion when compared to placebo, but a non-significant difference when compared with hyoscine butyl-bromide. Yanney et al. [44] compared diclofenac with two groups, finding diclofenac more effective than counselling only.

In six studies, the NSAID was considered the comparator rather than the intervention [28, 32, 41–44]. Castro et al. [28] found no difference in pain scores between intracervical anaesthesia and oral ibuprofen. de Oliveira et al. [32] compared naproxen with intracervical anaesthesia, finding the latter significantly better for pain during IUD insertion. Sääv et al. [41] compared sublingual misoprostol with diclofenac, finding no significant difference. Sakna et al. [42] compared 10% cervical lidocaine spray and oral ibuprofen, with the former significantly more effective at reducing insertion pain. Vitti et al. [43] compared 2% intracervical anaesthesia and oral ibuprofen, finding no difference between the two groups' mean pain scores. Whilst suppository diclofenac was more effective than the counselling only arm of their study, Yanney et al. [44] found both less effective in reducing pain during IUD insertion than 10% lidocaine spray.

Of the studies that did not find a statistically significant reduction in pain with NSAID during IUD insertion, four reported benefits at other time points [23, 36, 38, 39]. Abbas et al. [23] found a statistically significant reduction in pain during speculum and tenaculum insertion with oral diclofenac. Whilst unable to demonstrate a statistically significant reduction in pain at insertion, a statistically significant reduction in post-procedural pain was observed at ten minutes by Marcelino et al. [36] and at five and fifteen minutes for Ngo et al. [38, 39] Whilst Peerananrangsee et al. [40] found no significant difference in pain during IUD insertion between oral etoricoxib and placebo overall, a subgroup analysis of nulliparous women did demonstrate a significant reduction in IUD insertion pain.

Fourteen studies reported on medication safety and side effects [23–25, 27, 30–33, 35, 36, 38, 39, 42, 44]. Seven studies described the need for additional analgesia (Table 2) [23–25, 31, 37, 38, 42]. Other clinical outcomes and patient factors like parity and age were more inconsistently reported. Only two studies reported baseline pain conditions (endometriosis, dysmenorrhoea, pelvic pain and mental health conditions), with two studies including the percentage of patients with dysmenorrhoea [24, 25]; the remaining studies either did not report characteristics [23, 26, 29, 30, 33–35, 41] or excluded patients with these conditions from participation [27, 28, 31, 32, 36–40, 42–44].

3.5 | Results of Meta-Analyses

A meta-analysis of fourteen studies comparing NSAID and placebo was performed (Figure 2; Appendix B). One study comparing NSAID with placebo was excluded from the meta-analysis given an inability to appropriately convert pain measurements [27]. No other comparator group had sufficient studies to meta-analyse.

Included NSAIDs demonstrated a statistically significant reduction of 0.77 (95% CI −1.29, −0.25, $p=0.004$) in pain experienced during IUD insertion when compared to placebo, as measured on a 10 cm scale. This suggests a modest benefit when NSAIDs are used during IUD insertion. However, studies displayed significant heterogeneity ($I^2=88\%$, $p<0.001$) and GRADE certainty for evidence was low. Sensitivity analysis identified Hubacher et al. [34] had the most influence. Removing this study increased the overall reduction to 0.82 (95% CI −1.38, −0.26, $p=0.004$).

Subgroup analyses by drug type and dose strength (in which a high dose was defined as exceeding the single recommend dose) showed no significant differences between NSAID and placebo.

TABLE 2 | Secondary study outcomes.

	Need for additional analgesia (*n*)				Adverse outcomes (*n*)				Side effects (*n*)			
Source	**NSAID**	**Placebo**	**Comparator 1**	**Comparator 2**	**NSAID**	**Placebo**	**Comparator 1**	**Comparator 2**	**NSAID**	**Placebo**	**Comparator 1**	**Comparator 2**
Abbas et al., 2018 [23]	0	0			0	0			10	23		
Abbas et al. 2018 [24]	0	0			0	0			4	10		
Abbas et al. 2017 [25]	0	0			0	0			4	10		
Bednarek et al., 2015 [26]												
Beheiry et al., 2021 [27]					0	0	1	1	3	5	6	0
Castro et al., 2014 [28]												
Chor et al., 2012 [29]												
Crawford et al., 2017 [30]					0[a]	0[a]			0	0		
Darweesh et al., 2020 [31]	3	4	3		0	0	0		4	3	16	
de Oliveira et al., 2021 [32]					3		4					
Fahmy et al., 2016 [33]					1	1	2		11	2	0	
Hubacher et al., 2006 [34]												
Karabayirli et al., 2012 [35]					0	0	0		0	0	0	
Marcelino et al., 2024 [36]					0	1			1	3		
Miles et al., 2019 [37]	9	12	8	10								
Ngo et al., 2015 [38]	6	16			0	0			6	12		
Ngo et al., 2016 [39]					2	6			15	22		
Peerananrangsee et al., 2018 [40]												
Sääv et al., 2007 [41]									18		23	
Sakna et al., 2023 [42]	24	58			8		5					
Vitti et al., 2012 [43]												
Yanney et al., 2023 [44]					0		0	0	0		0	2

[a]Information obtained from clinical trial protocol findings.

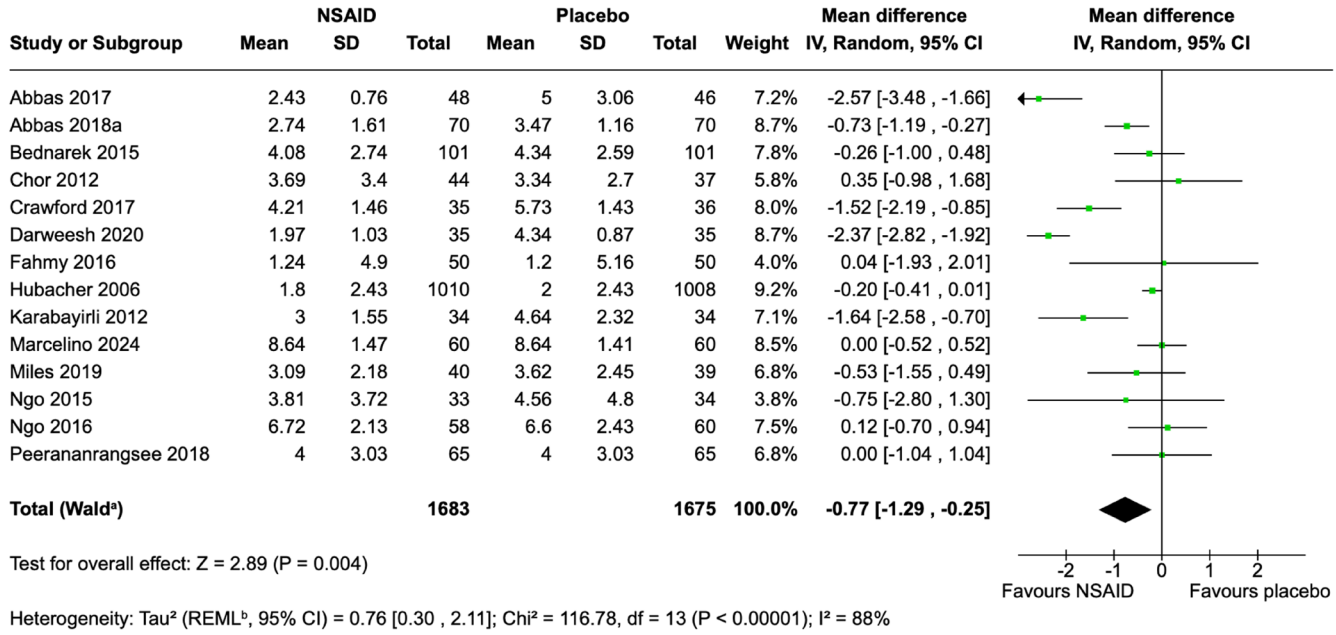

FIGURE 2 | Mean difference in pain on a 10 cm scale with NSAID compared to placebo. [a]CI calculated by Wald-type method. [b]Tau^2 calculated by restricted maximum-likelihood method.

TABLE 3 | Meta-regression analysis with outcome difference in pain score versus controls.

	Univariate coefficient (95% CI)	*p*	Adjusted coefficient (95% CI)	*p*
IUD type	−0.804 (−1.884, 0.275)	0.131	−1.374 (−4.508, 1.759)	0.311
Age	−0.0372 (−0.022, 0.015)	0.663	0.018 (−0.217, 0.253)	0.852
Parity	0.784 (−0.384, −1.952)	0.157	[a]	
Drug group	−0.396 (−0.828, 0.036)	0.069	0.147 (−1.481, 1.775)	0.826
Dose group	0.090 (−1.126, 1.307)	0.874	1.142 (−0.864, 3.148)	0.203
Timing of dose	0.001 (−0.042, 0.045)	0.954	0.040 (−0.035, 0.116)	0.229
Year of publication	−0.034 (−0.168, 0.100)	0.593	−0.160 (−0.712, 0.391)	0.488

[a]Parity unable to be explored in multivariate analysis due to the small number of studies reporting information.

Tests for subgroup differences were also non-significant ($\chi^2 = 5.46$, $p = 0.14$ for drug type and $\chi^2 = 0.05$, $p = 0.82$ for dose strength), providing no strong evidence for effect modification by NSAID subtype or dosing.

To explore sources of heterogeneity, meta-regression was conducted using effect size as the dependent variable (Table 3). The covariates drug dose, type and timing, parity (divided into high or low proportion nulliparous), IUD type (copper compared to LNG/mixed) and mean age were explored. No covariate was significant on univariate or multivariate analysis.

Of the fourteen studies comparing NSAID and placebo, nine studies reported adverse events and side effects; six studies [24, 25, 30, 31, 35, 38] had no adverse events and four [24, 25, 30, 35] no side effects. Whilst pooled analysis suggested a trend towards reduced odds of adverse events with NSAIDs (OR = 0.41, 95% CI 0.11, 1.51), this finding was not statistically significant ($p = 0.78$). Similarly, rates of side effects between NSAIDs and placebo were similar (OR = 0.92, 95% CI 0.35, 2.39, $p = 0.86$). GRADE certainty was very low.

4 | Discussion

4.1 | Interpretations

This systematic review and meta-analysis demonstrates that NSAIDs provide a modest reduction in pain during IUD insertion when compared to placebo. The mean reduction of 0.77 on a 10 cm scale (95% CI −1.29, −0.25), whilst statistically significant, represents a relatively small practical difference. A systematic review and meta-analysis of 37 studies by Olsen et al. [45] found the minimal clinically important difference (MCID) in acute pain varied greatly and was influenced by several factors such as baseline pain and clinical context; they suggested a MCID of 1.7 cm was clinically significant. Our finding of a reduction of < 1 cm suggests that whilst there is a demonstrated statistical

significance with NSAIDs for the management of IUD insertion pain, the clinical impact may be modest or imperceptible.

Subgroup analysis by individual NSAID type failed to demonstrate a significant difference between groups. This may suggest the associated studies lack sufficient statistical power.

There is evidence for high dose NSAID use in medical termination of pregnancy (MTOP), where 1600 mg ibuprofen was shown to reduce pain scores by 2.26 points (95% CI −3.00, −1.52) when compared to 2000 mg paracetamol [46]. Our analysis by dose strength found no significant between-group differences when comparing high and low dose cohorts, though the maximum dose of ibuprofen in included studies was 800 mg.

Rates of adverse events and side effects were similar across the NSAIDs and placebo groups. This indicates that the use of NSAIDs does not result in a significant increased risk of medication-related effects.

Our findings differ from previous systematic reviews that concluded there was limited or inconsistent evidence for NSAID efficacy in IUD insertion pain. This may be through the addition of newer studies that demonstrated benefit and/or the completion of a meta-analysis to pool smaller studies. Instead, they are more consistent with the evidence for MTOP, in which there is demonstrated superiority for ibuprofen in reducing abortion pain when compared to non-NSAID alternatives [46]. As such, we argue that it is reasonable to use NSAIDs for the management of IUD insertion pain.

4.2 | Limitations

Findings should be interpreted in the context of multiple limitations. There was significant heterogeneity ($I^2 = 88\%$) of studies included in the meta-analysis, which reflects observed variances in study design. Study NSAIDs varied considerably, including in drug, dose, route and timing of administration. Studies also differed in their comparator (from placebo to opioid, local anaesthesia or prostaglandin analogue). Factors likely to contribute to pain perception, including conditions like endometriosis and chronic pelvic pain, were rarely reported, with many studies excluding these patients from study participation. This may limit generalisability of findings to the broader cohort of patients undergoing IUD insertion.

Additionally, pain measurement methods differed across studies, with the VAS and NRS most commonly used. There is some evidence to suggest that participants rating their pain tend to score pain higher on the NRS, though this research is in a non-gynaecological context [47, 48]. It is likely that variances in pain measurement contribute to study heterogeneity, further limiting finding quality.

Study quality was variable, and two studies were deemed at high risk of bias. Many of the included studies had small sample sizes, limiting their ability to detect meaningful differences in pain. The inclusion of one large study [34] resulted in an overall sample size of 3358—and unsurprisingly, sensitivity analysis identified this study to exert the most influence on meta-analysis findings, which were deemed to be of low quality.

Whilst not detected in statistical analysis, publication bias remains a concern given that small negative studies may be less likely to be published. The predominance of studies from certain geographical regions (particularly Egypt and the United States) may limit generalisability to other healthcare settings with different populations or procedural approaches.

4.3 | Implications

In contrast to existing literature, our systematic review and meta-analysis identified a role for NSAIDs in IUD insertion pain management through a statistically significant reduction in pain. However, current evidence quality is low and limited by small sample size, single-centre studies and inconsistent pain assessment and measurement.

NSAIDs are commonly used and recommended in guidelines despite limited evidence because of their low cost and excellent safety profile. Our findings provide an evidence base for this use during IUD insertion. Clinicians should counsel patients that whilst NSAIDs may provide some benefit, as a single agent they are unlikely to eliminate insertion pain entirely. NSAIDs should be viewed as one component of comprehensive pain management.

5 | Conclusion

This systematic review and meta-analysis aimed to identify and analyse current evidence relating to NSAID analgesia use during outpatient IUD insertion. Twenty-two RCTs meet inclusion criteria and were analysed. Meta-analysis of fourteen studies found a moderate, statistically significant reduction in pain during IUD insertion with an NSAID when compared to placebo (mean reduction 0.77, 95% CI −1.29 to −0.25). However, the certainty of this evidence was rated low using GRADE, due to risk of bias, inconsistency ($I^2 = 88\%$) and imprecision.

Future studies should be large, multi-centre RCTs using standardised pain assessments. Inclusion of secondary outcomes such as need for additional analgesia and safety profiles of medications would further improve quality of evidence and subsequent recommendations for practice. Research using a combination of NSAID and non-NSAID analgesia may also better reflect current practice and result in a more clinically meaningful reduction in pain. Until such evidence is available, NSAIDs remain a reasonable first-line option for management of IUD insertion pain.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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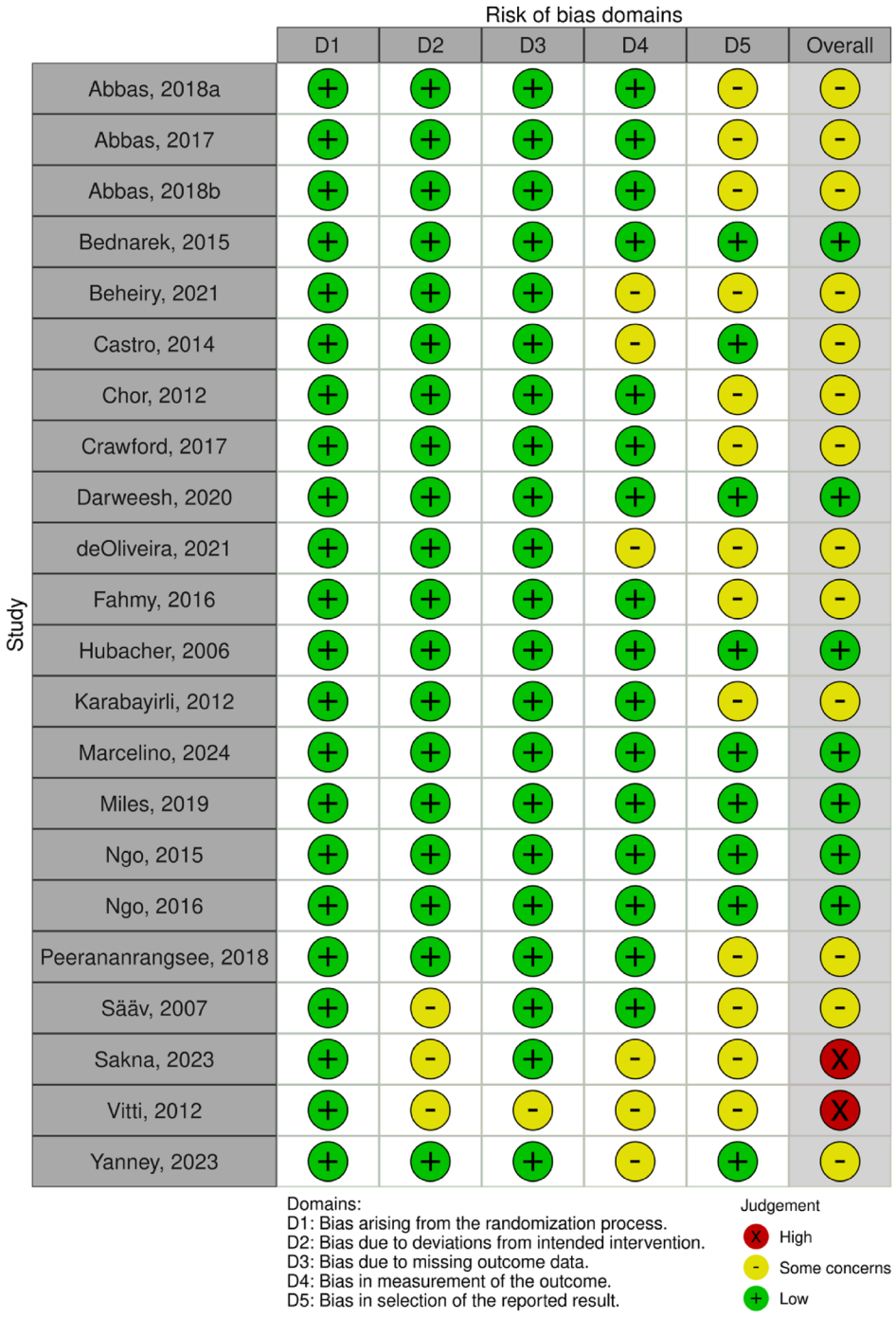
Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Information: S1.** PICO framework. **Supporting Information: S2.** Search strategy.

Appendix A

Risk of Bias 2 (RoB 2) Assessment [20]



Appendix B

Summary of the Results for the Effect of Intervention on Pain Experienced During IUD Insertion

Outcomes	Studies (*n*)	Sample size (*n*)	Mean difference (95% CI)	Heterogeneity ([%] 95% CI)	Egger's test	Evidence quality	GRADE [21, 22]
Pain reduction on 10-point scale: NSAIDs compared to placebo	14	3358	−0.77 (−1.29, −0.25)	88.8 (42.4, 95.4)	0.454	⊕⊕◯◯ Low	Risk of bias: No[a] Inconsistency: Very serious Indirectness: No Imprecision: No Publication bias: No[b]

Outcomes	Studies (*n*)	Sample size (*n*)	Relative effect (95% CI)	Heterogeneity ([%] 95% CI)	Egger's test	Evidence quality	GRADE
Adverse events: NSAID compared to placebo	9	338[c]	0.41 (0.11, 1.51)	0 (0.0, 18.8)	0.645	⊕◯◯◯ Very low	Risk of bias: No Inconsistency: Serious Indirectness: No Imprecision: Very serious Publication bias: No[d]
Side effects: NSAID compared to placebo	9	475[c]	0.92 (0.35, 2.39)	60.3 (0.0, 86.4)	0.571	⊕◯◯◯ Very low	Risk of bias: No Inconsistency: Very serious Indirectness: No Imprecision: Very serious Publication bias: No[d]

[a] No high-risk studies included in sample; plausible bias unlikely to seriously alter the results.
[b] Egger's test showed no small study effects; on visual inspection, funnel plot not skewed.
[c] Nine studies included reporting on adverse events and side effects, sample size represents total sample of studies with events.
[d] Egger's test showed no small study effects.