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A systematic review of copper intrauterine contraception continuation in young nulliparous women based on IUD type

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TITLE PAGE

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on IUD type

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Short Title: Review of IUD continuation rates in young nulliparous women

ABSTRACT

Objectives

To undertake a systematic review to determine which IUDs are associated with higher continuation rates in younger aged nulliparous women. IUD continuation rates based on type was the main outcome, with reasons for IUD discontinuation as secondary outcomes.

Methods

Electronic databases from their inception to date (7.2.2021) and relevant websites were searched using search terms 'copper intrauterine', 'copper intrauterine device', 'copper coil', 'copper IUD' and 'copper T' for articles published in English. Screening titles, abstracts and then full texts for eligibility, quality appraisal and data extraction were independently performed in duplicate. The Mixed Methods Appraisal Tool was used to assess quality and meta-analysis performed where available data was amenable to quantitative synthesis.

Results

Nineteen studies reported on IUDs available or comparable to those available to young and nulliparous women in the UK. The highest continuation rates were reported with smaller-sized IUDs. These were the TCu 380A Nul (91.3%), Multiload Cu 375 sl (89%), and Mini TT380 slimline (86.8%). Meta-analysis showed the standard-sized Cu T380A IUD was associated with good continuation at 12 months (weighted average 71.6%-81.9%) but higher discontinuation related to bleeding/pain and expulsion compared to smaller IUDs. IUDs with flexible arms (Nova T, Multiload) were also associated with higher continuation and lower removal rates for bleeding/pain and expulsion compared to IUDs with rigid arms (Cu T or TCu).

Conclusions

Evidence for IUD use in younger aged nulliparous women based on IUD type remains limited. More research is needed to better determine which current IUD types have higher continuation rates and fewer unwanted effects in this group of IUD users. Identifying IUDs better suited to these women could improve their user satisfaction, continuation rates and sexual health.

PROSPERO registration number CRD42019120969.

SHORT TITLE: Review of IUD continuation rates in young nulliparous women

KEY WORDS: IUD, continuation, discontinuation, reasons, young, nulliparous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first reported systematic review exploring IUD types in younger aged nulliparous women
- A wide range of data sources unrestricted to randomised controlled trials was reviewed – an approach more representative of the real world
- Articles for inclusion were limited to publications in the English language
- Some data was obtained by calculation and measurements of graphs or figures where this was not numerically specified in reports
- Most studies did not differentiate between nulligravid and nulliparous participants

REPORTING STATEMENT CHECKLIST

See supplementary material 1

MAIN TEXT: (4366 words)

INTRODUCTION

The highest rates of unintended pregnancy and terminations of pregnancy, which contribute to poor sexual health, are in women aged 20-24 followed by those aged 25-29.[1] Increasing uptake of long-acting reversible contraceptives (LARC) like copper intrauterine contraception in these women is yet to yield a proportional reduction in pregnancy terminations, attributable to their higher LARC discontinuation rates.[2]

Copper intrauterine contraception is the LARC with the greatest number of brands, with 21 copper intrauterine devices (IUDs) available in the UK.[3] IUDs are of various shapes, sizes, total copper surface area and copper distribution on the IUD frame. They have changed little over the last 40 years. No IUD type has been shown to be associated with better outcomes regarding continuation or unwanted effects that lead to early IUD discontinuation. Early IUD discontinuation excludes discontinuation due to IUD user choice alone or the wish to conceive. IUD continuation rates tend to be surrogate for IUD satisfaction and/or acceptability. Studies have shown IUD continuation to be lower with unfavourable outcomes related to unwanted effects in adolescents and women in their 20s compared to their older parous counterparts.[4-6]

Previous systematic reviews and guidance suggest that IUD size and shape may be a factor in discontinuation and have recommended future research investigate which IUD types are associated with less pain, bleeding and discontinuation.[7-10] The identification and use of those

IUDs associated with higher continuation and fewer unwanted effects could improve outcomes including IUD satisfaction and continuation rates in younger aged nulliparous women.

Consequently, a systematic review and meta-analysis was therefore undertaken to investigate continuation rates and reasons for discontinuation of IUDs currently available or comparable to those currently in use in the UK based on IUD type in women aged under 30.

OBJECTIVES

To determine which currently available IUDs are associated with higher continuation rates in young and nulliparous women aged under 30 by systematically reviewing published studies. Discontinuation rates and reasons for discontinuation were secondary outcomes. Where studies on IUDs currently available in the UK were lacking, studies with IUDs comparable in shape, size, total copper surface area or distribution on the IUD frame to those currently available in the UK were to be included for review.

METHODS

An appraisal of previous systematic reviews including publications by the Cochrane Collaboration Fertility Regulation Group, Faculty of Sexual and Reproductive Healthcare (FSRH) and National Institute for Health and Care Excellence (NICE) was performed. A search strategy was developed in conjunction with an Electronic Services Librarian. These informed the design of this systematic review and its protocol.

This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline. Its protocol was registered on the International Prospective Register of Systematic Reviews database (PROSPERO; CRD42019120969, see supplementary material 2).[11] The protocol included an approach to consider other studies besides randomised controlled trials (RCTs) that report on IUD continuation if the RCTs determined eligible for inclusion in the systematic review were too few to address the review question.

Selection criteria

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved IUDs available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over 30, that involved IUDs not available, or not of the same design and size to those available, in the UK.

Search Strategy

Nine electronic databases - the Allied and Complementary Medicine (AMED), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Nursing and Allied Health Professionals Database (EMCARE), Health Management Information Consortium (HMIC), General Medical Database (MEDLINE), Psychology

and Allied Fields (PsychINFO), and PubMed – were searched using search terms (copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab from database inception to 7 February 2021. The following additional sources were searched using the term 'Copper intrauterine': the Cochrane Library, Database of Abstracts and Reviews of Effects (DARE), Turning Research into Practice (TRIP) database, National Electronic Library of Health (merged with MEDLINE), Bandolier, Medicines and Healthcare products Regulatory Agency, FSRH, Royal College of Obstetricians and Gynaecologists, Department of Health, NICE, Scottish Intercollegiate Guidelines, and World Health Organisation websites. A Google Scholar search was also undertaken using the term 'Copper intrauterine device young nulliparous'.

Relevant articles published in the English were identified by two authors and these exported into an Endnote library upon completion of searches. Following de-duplication, the relevant articles obtained from searches were exported to Rayyan, a web app for systematic reviews (rayyan.ai). In Rayyan, further de-duplication yielded unique entries of which abstracts, and then full texts, were screened independently by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. Additional citation screening of reference lists of both included and excluded studies was performed. Screening was initially done in batches of 20, then later increased to 50. Agreements were obtained between the first two authors and did not require a third review. Selected articles were randomised controlled trials (RCTs) and observational studies published in English involving IUDs available or comparable to those in the UK involving nulliparous participants aged under 30.

Quality Assessment and Data Summary

All articles selected for inclusion in the systematic review underwent a quality assessment using the Mixed Methods Appraisal Tool version 2018 (MMAT).[12] The MMAT risk of bias tool was chosen because it was applicable to all the study types of articles selected for inclusion. The highest possible total MMAT score conforming with best quality was seven, while the lowest possible score for poor quality was zero. Included articles were initially quality assessed by the two authors separately and then agreement reached.

Data extracted from articles included IUD type, study location(s) and year of publication, age of women, gravidity/parity of women, IUD continuation and discontinuation rates, and reasons for IUD discontinuation. Where a rate was not specified but could be calculated, this was done to one decimal place. If a continuation rate had not been specified, this was obtained by adding all stated rates for reasons for discontinuation and subtracting from 100. If a discontinuation rate was not specified, this was obtained by subtracting a stated continuation rate from 100, or by adding all stated rates for reasons for discontinuation. Gross rates (obtained after excluding participants lost to follow up or removals to conceive) were used, except where only net cumulative rates were reported. Measurements were performed to obtain data from published graphs or figures where rates had been reported in this format but not numerically specified.

An Excel data collection form was developed, piloted with three articles selected for inclusion by one author, then revised and amended by the second author before proceeding to data

extraction. Data from the 19 selected articles included in the review was extracted by one author unto the Excel spreadsheet and checked by the second author.

Data Analysis

Where available data was amenable to quantitative synthesis, random effects meta-analyses of proportions were performed using the metaprop suite of commands on STATA 16. Variances were stabilised using the Freeman-Tukey double arcsine transformation. Where possible, subgroup analysis was performed to examine differences between nulliparous women aged ≤30 years and nulliparous women of any age. Statistical heterogeneity was reported using the I^2 statistic, and the effect of removing individual studies on the overall effect size was explored in sensitivity analyses (supplementary material 3). Publication bias was examined by producing Doi plots and generating LFK index values, considered a more appropriate measure of publication bias than funnel plots/Egger's test when performing meta-analyses of proportions.[13]

Patient and Public Involvement

The Faculty of Sexual and Reproductive Healthcare (FSRH) is the UK organisation committed to meeting the highest SRH standards, ensuring improvements in population SRH and supporting SRH professionals. The FSRH's Contraceptive Priority Setting Partnership in liaison with the James Lind Alliance yielded over 700 responses from patients, practitioners and the public that identified 'Which interventions increase uptake and continuation of effective contraception including long-acting methods…?' as the top SRH research priority.[14] This influenced the research aims. IUD users attending a sexual health clinic over a four-week period were consulted about improving access to and use of intrauterine contraception. Their suggestions, which included studying women's experiences with IUDs, were used in developing the research question, aims, and study design. The Consumer Panel of the North East Research Design Service was also consulted and the proposed research presented to them. The research plan was modified in line with their feedback.

Ethics Approval Statement

This study does not involve human participants and does not involve animal subjects. It was therefore exempt from Research Ethics Committee review.

RESULTS

Only one study, a prospective (non-RCT) cohort, provided information on an IUD available in the UK solely involving nulliparous users aged under 30.[15] This was inadequate to address the review question. So as per the systematic review protocol, other studies on IUDs currently available in the UK or IUDs comparable (same design and size) to those available in the UK (Box 1) involving nulliparous women of all ages (so not limited to those aged under 30) were also screened.

Box 1 – Characteristics of IUDs in included studies

IUD brand / name	Copper (mm^2)	shape / design	width (mm)	arms' flexibility
Currently available in the UK				
Cu T380A / TCu 380A / TT380 Slimline	380	T with arm bands	>30	No
TCu 380A Nul / Mini TT380 slimline	380	T with arm bands	23.2	No
Multiload Cu 375	375	Ω	16 – 20.5	Yes, flex down
Nova T 380	380	T without arm bands	>30	Yes, flex up
Comparable to those available in the UK				
Nova T 200	200	T without arm bands	≥30	Yes, flex up
TCu 300	300	T without arm bands	>30	No
Cu T200 / TCu 200	200	T without arm bands	>30	No
TCu 220C	220	T without arm bands	>30	No

Thirty records were obtained upon this expansion and their full texts assessed. Eleven records were excluded for lack of usable outcome data (n=8; [5, 16-22]) and their full texts unobtainable (n=3; [23-25]) (see supplementary material 4). A total of 19 studies on IUDs available or comparable to those available in the UK in nulliparous women were eventually obtained and included in the systematic review (Table 1).[15, 26-43] Figure 1 depicts a PRISMA flow diagram detailing the search and selection process.[44]

Table 1 – Characteristics of Included Studies

Study / Authors	Year	Country	Study Design	Study Objectives	IUDs in study	Quality (MMAT score)
Abraham et al [15]	2015	USA	Prospective cohort	Relationship among young age, nulliparity, and continuation of long-acting reversible contraceptives	Copper T380A	Good (7)
Akintomide et al [26]	2019	UK	Retrospective records review	Discontinuation rates and reasons for discontinuation at 1 year of the small-sized Mini TT380 Slimline IUD compared with the standard-sized TT380 Slimline	Mini TT380 slimline TT380 slimline	Good (6)
Allonen et al [27]	1980	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 2 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (6)
Elkhateeb et al [28]	2020	Egypt	Prospective cohort	Acceptability of IUD use in nulliparous women by both women and health care providers	Copper T380A	Good (7)
Fugere [29]	1990	Canada	Prospective cohort	Clinical performance of the Nova T200 IUD over 5 years	Nova T200	Good (7)
Hall and Kutler [30]	2016	USA	Prospective cohort	Experience and satisfaction of nulliparous intrauterine contraception users at 1, 6, 12 and 18 months	Copper T380A	Good (7)
Kaislasuo et al [31]	2015	Finland	Prospective cohort	Menstrual characteristics and ultrasonographic uterine cavity measurements predict bleeding and pain in nulligravid women using intrauterine contraception	Nova T380	Good (7)
Larsen et al [32]	1981	Denmark	RCT – patient blind	Comparison of clinical performances of Progestasert and Copper T200 at 12 months	Copper T200	Good (5)
Lewit [33]	1973	USA	Prospective cohort	Two years' experience of the Copper T200	Copper T200	Good (7)
Liedholm and Sjoberg [34]	1974	Sweden	Prospective cohort	Two years' experience with the Copper T200 and comparison between nulliparous and parous women	Copper T200	Good (7)
Luukkainen et al [35]	1979	Denmark, Finland Sweden	RCT – double blind	Experience and clinical performance of the Nova T200 and Copper T200 at 12 months	Nova T200 Copper T200	Good (6)
Luukkainen et al [36]	1987	Denmark, Finland, Hungary, Norway, Sweden	RCT – no blinding	Use-effectiveness and clinical performance of levonorgestrel- and copper-releasing intrauterine devices at 12 months	Nova T200	Good (6)
Mishell et al [37]	1973	USA	Prospective cohort	Continuation and clinical performance of TCu 200 in nulliparous women	Copper T200	Good (7)
Nygren et al [38]	1981	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 3 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (7)

Ostergard and Gunning [39]	1979	USA	RCT – blinding not stated	Continuation and clinical performances of Copper T200 and Dalkon Shield in nulligravid women at 12 months	Copper T200	Good (5)
Otero-Flores et al [40]	2003	Mexico	RCT – single (patient) blind	Comparison of clinical performance of three different IUDs in nulliparous women	Copper T380A Copper T380A Nul Multiload 375 sl	Good (6)
Roy et al [41]	1974	USA	Prospective cohort	Experience with three different IUD models in nulliparous women at 1 year	Copper T380A Copper T300 Copper T200	Good (7)
Sivin and Stern [42]	1979	USA	RCT – double blind	Experience of three different IUDs in nulliparous and parous women	Copper T380A Copper T220C Copper T200	Good (5)
Timonen et al [43]	1974	Finland	Prospective, single (patient) blind	Use-effectiveness of Copper T300 at 1 year	Copper T300	Good (7)

All included studies were generally of good quality (mean 6.42 [5-7]). The lowest MMAT score of 5 obtained was for three RCTs published in 1979 and 1981, possibly related to inadequate reporting (Table 2).[32, 39, 42] Their reports did not confirm that randomisation had been appropriately performed, [32, 42] randomised groups were comparable at baseline, [39, 42] nor that outcome assessors were blinded to the intervention provided [32, 39].

Although the outcome data obtained was considered homogenous, studies' designs, participant ages and parity, and IUD types were not; making a quantitative synthesis of the outcome data in totality inappropriate. Results were therefore grouped into three to include studies involving: 1. IUD types currently available in the UK and only nulliparous women aged ≤30; 2. IUD types currently available in the UK and nulliparous women of all ages; 3. IUD types comparable to those available in the UK and nulliparous women of all ages. (Table 3)

Table 2 – Quality Assessment of Included Studies Using the Mixed Methods Appraisal Tool (MMAT) version 2018 [12]

Study / Authors	*Design Category*	*Responses to MMAT Questions (and Scores: Yes (1) / No (0) / Can't Tell (0)*							
		Screening 1	**Screening 2**	**Appraisal 1**	**Appraisal 2**	**Appraisal 3**	**Appraisal 4**	**Appraisal 5**	**Total**
Abraham et al [15]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Akintomide et al [26]	Quantitative, non-randomised	yes	yes	yes	yes	no	yes	yes	6
Allonen et al [27]	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Elkhateeb et al [28]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Fugere [29]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Hall and Kutler [30]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Kaislasuo et al [31]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Larsen et al [32]	Quantitative, randomised	yes	yes	can't tell	yes	yes	no	yes	5
Lewit [33]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Liedholm and Sjoberg [34]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Luukkainen et al [35]	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Luukkainen et al [36]	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Mishell et al [37]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Nygren et al [38]	Quantitative, randomised	yes	yes	yes	yes	yes	yes	yes	7

Ostergard and Gunning [39]	Quantitative, randomised	yes	yes	yes	can't tell	yes	no	yes	5
Otero-Flores et al [40]	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Roy et al [41]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Sivin and Stern [42]	Quantitative, randomised	yes	yes	can't tell	can't tell	yes	yes	yes	5
Timonen et al [43]	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7

Table 3 – Summary of Findings

Study	IUD types (N[µ])	Ages at insertion (y)	Study period	Continuation rates % (n)[CI]	Discontinuation rates % (n)	Removal for bleeding/pain % (n)	Expulsion % (n)	Pregnancy % (n)
Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30								
RCT								
Otero-Flores et al 2003 [40] [§]	TCu 380A (375) TCu 380A Nul (367) ML Cu 375 sl (374)	23.2±6.8 22.4±6.6 22.6±6.4	12 months	30.7 (115) 91.3 (335) 89.0 (333)	69.3 (260) 8.7 (32) 11.0 (41)	61.6 (231) 3.81 (14) 6.68 (25)	3.47 (13) 1.91 (7) 1.87 (7)	1.07 (4) 0.54 (2) 0.00 (0)
Non-RCT								
Abraham et al 2015 [15]	Cu T380A (201) Cu T380A (44) Cu T380A (201) Cu T380A (44)	20 - 25 <20 20- 25 <20	12 months 24 months	82 [76-87] 79 [64-89] 73 [66-79] 64 [48-77]	ns ns	ns ns	ns ns	ns ns
Hall and Kutler 2016 [30]	Cu T 380A (21)	18 - 30	12 months	73.7 (14)	26.3 (5)	10.5 (2)	10.5 (2)	5.26 (1)
Studies of IUD types currently available in the UK involving nulliparous women of all ages								
RCTs								
Sivin and Stern 1979 [42][¶,a]	TCu 380A (2254) TCu 220C (1301) TCu 200 (4215)	<20 - 35+ <20 - 35+ <20 - 35+	2y	55.7 57.8 54.2	44.3 42.2 45.8	21.9 19.5 16.8	7.8 9.8 9.8	0.8 1.6 5.1
Non-RCTs								
Akintomide et al 2019 [26]	TT380 Slimline (27) Mini TT380 Slimline (53)	15 – 37 16 - 37	1y	66.7 (18) 86.8 (46)	33.3 (9) 13.2 (7)	ns ns	3.7 (1) 3.77 (2)	0 (0) 0 (0)
Elkhateeb et al 2020 [28]	TCu 380A (90)	16 - >30	6 months	94.4 (85)	5.6 (5)	ns	0 (0)	ns
Kaislasuo et al 2015 [31][§]	Nova T380 (42)	18 - 43	1y	83.3 (35)	16.7 (7)	ns	4.76 (2)	ns
Roy et al 1974 [41]	TCu 380A (785) TCu 300 (347) TCu 200 (472)	<14 - >33 15 - >33 <14 - >33	12 months	81.9 80.7 74.2	18.1 19.3 25.8	9.1 9.2 10.7	3.8 6.1 5.4	0.2 0.6 1.7

Studies of IUD types comparable to those available in the UK involving nulliparous women of all ages								
RCTs								
Luukkainen et al 1979 [35][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	12 months	ns ns	ns ns	15.3 23.4	6 10.8	0.53 2.3
Allonen et al 1980 [27][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	24 months	ns ns	ns ns	23.5 24	6.5 14	1.14 5.28
Nygren et al 1981 [38][a]	Nova T200 (ns) Cu T200 (ns)	<20 - >35	36 months	36.9 31.0	ns ns	28.3 (24) 28.2 (28)	10.3 (27) 10.7 (26)	1.5 (4) 6.5 (15)
Larsen et al 1981 [32][a]	Cu T200 (99)	15 - 44	12 months	73	27[α]	16	5	1
Luukkainen et al 1987 [36]	Nova T200 (77)	17 – 40	12 months	73.1	26.9[α]	10.4	9.2	0
Ostergard and Gunning 1979 [39]	TCu 200 (117) TCu 200 (115)	18 – 34	6 months 12 months	88.9 (104) 73.0 (84)	11.1 (13) 27.0 (31)	6.0 (7) 12.2 (14)	3.41 (4) 6.09 (7)	0 (0) 0 (0)
Non-RCTs								
Fugere 1990 [29]	Nova T200 (54)	17 - 42	24 months	ns	ns	17.2	1.9	0
Lewit 1973 [33]	TCu-200 (2099) Nulligravid subgroup: TCu-200 (1585)[§] Age subgroups: TCu-200 (1130) TCu-200 (2468) TCu-200 (1513) TCu-200 (683) TCu-200 (449)	15-49 15-49 15 – 19 20 – 24 25 – 29 30 – 34 35 - 49	1y 1y 1y 1y 1y 1y 1y	73.3 75.9 67.3 73.8 77.6 81.7 85.2	26.7 24.1 32.7 26.2 22.4 18.3 14.8	9.4 9.6 7 8.3 5.8 7.9 6.8	10.7 8.7 15 8.5 8.7 6 3.1	1.3 0.8 2.3 2.8 1.5 0.4 0.3
Liedholm and Sjoberg 1974 [34]	T-Cu 200 (208) `	14 - 40	12 months 24 months	70.2 60.3	29.8 39.7	18.1 28	0.5 0.5	2.9 (6) 2.9 (6)
Mishell et al 1973 [37][a]	TCu 200 (471)	14-33	3 months 6 months 12 months	92.6 84.5 74.2	7.4 15.5 25.8	2.8 5.8 10.7	2.6 4.7 5.4	0.2 0.4 1.7
Timonen et al 1974 [43]	T Cu-300 (138)	<25 - 40+	12 months	84.7	15.3	7.2	1.6	1.6

RCT – randomised controlled trial; ns – not stated; μ - sample size or participants excluding those lost to follow up or removals to plan pregnancy; § - nulligravid women only; ¶ - a combination of double blind studies; α – not stated; obtained by subtraction of continuation rate from 100 a – net cumulative rates; b – data obtained from graphs or figures

Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30

The Copper T380A IUD (TCu 380A or Cu T380A) type was associated with good continuation at 12 months in nulliparous women of all ages (weighted average 81.9% from four studies [15, 26, 30, 41]) as well as those ≤30 years (average 81.6%, from two studies [15, 30]). (Figure 2) Individual studies showed the TCu 380A had higher discontinuation related to bleeding/pain and expulsion [30, 40, 42] when compared to IUDs of smaller size or those with flexible arms [26, 40](Table 3). Continuation was also higher with age at 12 and 24 months when nulliparous TCu 380A IUD users aged <20 and 20 - 25 were compared (Table 3).[15]

Studies of IUD types currently available in the UK involving nulliparous women of all ages

Five studies reporting data pertaining to seven population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the TCu 380A IUD at 12 months post insertion.[15, 26, 30, 40, 41] The data of obtained from Otero-Flores et al (2003) was an outlier[40]. The TCu 380A was associated with good continuation at 12 months in nulliparous women of any age with a weighted average 71.6% (95% CI 51.15-88.44%, see Figure 3, when the Otero-Flores et al data was included) to 81.9% (95% CI 79.66-84.09%, see Figure 2, excluding Otero-Flores et al data).

Three studies - Abraham et al (2015), Hall and Kutler (2016) and Otero-Flores et al (2003) - reported on IUDs in women aged ≤30 involving the TCu 380A.[15, 30, 40] When the Otero-Flores et al data was included in this TCu 380A meta-analysis, nulliparous women ≤30 years of age at 12 months had a continuation rate of 66.9% [95% CI 32.09-93.90%], which was less than 80.9% [95% CI 76.04-85.48%] obtained for nulliparous women of any age (Figure 3). When the Otero-Flores et al data was excluded, nulliparous women aged ≤30 were similarly likely to continue to use the TCu 380A IUD at 12 months as observed with nulliparous women of any age (81.6% [95% CI 76.52-86.21%] versus 80.9% [95% CI 76.04-85.48] respectively) (Figure 2). Additionally, statistical heterogeneity using the I^2 statistic was found to be low/absent but was not statistically significant (I^2 = 0.00%, p = 0.47). Sensitivity analysis confirmed that the overall effect size was largely robust to the exclusion of individual studies (-1.01% to +0.21% change in effect size, see supplementary material 3). An LFK index value of 6.77 identified major Doi plot asymmetry consistent with publication bias (see supplementary material 5).

The highest continuation rates at 12 months were reported with smaller-sized IUDs - the Copper 380A Nul (TCu 380A Nul - 91.3%), Multiload Copper 375 sl (ML Cu 375 sl - 89%), and Mini TT380 slimline (86.8%)(Table 3). This data was obtained from only two studies whose participants were aged 15 to 37.[26, 40] Meta-analysis of continuation rate data on the TCu 380A Nul/Mini TT380 slimline IUD type gave a weighted average of 91% (95%CI 88.01-93.64)(Figure 4). These smaller IUDs were also associated with the lowest rates of removals for bleeding/pain (3.80 – 6.68%) and expulsion (1.87 – 3.77%) reported in nulliparous women at 12 months (Table 3).

STUDIES of IUD types comparable to those in the UK involving nulliparous women of all ages

Two studies reported data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T300 IUD (TCu 300) at

12 months post insertion [41, 43], reporting an overall effect size of 81.9% (95% CI 78.35-85.24%, see Figure 5).

Seven studies reporting data pertaining to 11 population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T200 IUD (TCu 200 or Cu T200) at 12 months post insertion, with a weighted average of 75.4% (95% CI 72.32-78.43%, see Figure 6).[32-34, 36, 37, 39, 41] These were also amenable to meta-analysis examining the proportion of women discontinuing the TCu 200 at 12 months post insertion due to bleeding and/or pain, reporting an overall effect size of 10.8% (95% CI 7.98-14.15%) as well as the proportion of women discontinuing the TCu 200 at 12 months post insertion due to expulsion, reporting an overall effect size of 6.4% (95% CI 4.49-8.69%) (see supplementary material 4). For these meta-analyses, nulliparous women aged <30 years compared to nulliparous women of any age at 12 months were found to be less likely to: continue to use the TCu 200 (73% [95% CI 67.63-78.10%] versus 76.5% [95% CI 72.67-80.14%]), discontinue the TCu 200 due to bleeding and/or pain (7% [95% CI 5.59-8.65%] versus 12.7% [95% CI 8.48-17.78%]), and discontinue the TCu 200 due to expulsion (10.52% [95% CI 7.17-14.41%] versus 4.93% [95% CI 2.93-7.39%]) respectively. However, none of these differences were found to be statistically significant. Statistical heterogeneity using the I^2 statistic were all found to be substantial. Sensitivity analyses confirmed that the overall effect sizes were largely robust to the exclusion of individual studies. In all cases, their LFK index values identified major Doi plot asymmetry consistent with publication bias (see supplementary material 5).

Continuation was seen to progressively improve with age where Lewit (1973) reported rates in nulliparous TCu 200 users by age groups 15 – 19, 20 – 24, 25 – 29, 30 – 34, and 35 – 49.[33] (Table 3)

Two studies reported data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Nova T200 at 12 months post insertion,[35, 36] reporting a weighted average of 73.2% (95% CI 70.10-76.22%, see supplementary material 5).

Studies also showed IUDs with flexible arms (Nova T, Multiload)[27, 35, 40] were associated with higher continuation and lower removal rates for bleeding/pain, expulsion and pregnancy where compared to IUDs with rigid arms (Cu T or TCu). (Table 3).

DISCUSSION

Findings and Interpretation

Evidence on IUDs currently used in nulliparous women aged under 30 is limited. These findings estimate the continuation rate for the recommended TCu 380A IUD [10] to be 81% at 12 months post insertion based on four studies involving young nulliparous women.[15, 26, 30, 41] This was the same estimate for the TCu 300 based on two studies.[41, 43] Smaller sized and flexible IUDs may be associated with higher continuation rates of 86-91% in this group of women based on two studies as well as fewer removals for bleeding/pain and expulsion compared to the TCu 380A or IUDs of same rigid design or size.[26, 40] Lower continuation rates of 75% and 73% were obtained for the TCu T200 and Nova T200 based on eight studies.[32-37, 39, 41]

The study by Otero-Flores et al was the only reported RCT at 12 months to solely consider IUDs currently used in the UK and involve younger aged nulliparous women.[40] Over a thousand nulliparous women aged 15 to 30 were randomised to receive three different IUDs - TCu 380A (32mmx36mm), TCu 380A Nul (23mmx29mm) and ML Cu 375 sl (≤20mmx29mm), the latter two of which were primarily designed for nulliparous women. The TCu 380A rates of discontinuation (69.3%) and bleeding/pain as reasons for discontinuation (61.6%) were significantly higher than for TCu 380A Nul (8.7% and 3.81%) and ML Cu 375 sl (11.0% and 6.68%), as well as significantly different from rates reported by other included studies involving the TCu 380A. This could be because the TCu 380A considerably differs in size from the TCu 380A Nul and ML Cu 375 sl IUDs, and Otero-Flores et al also exclusively involved nulligravid participants (as opposed to nulliparous).

Sivin and Stern (1979) was the only other RCT involving a TCu 380A that reported separately on nulliparous users.[42] However, their TCu 380A discontinuation and bleeding/pain rates, 44.3% and 21.9% respectively, were obtained at two years and their participants aged <20 to 35+.

The disparity in discontinuation rates reported by Otero-Flores et al [40] and Sivin and Stern [42] in addition to criticism for inaccuracies have suggested that the findings by Otero-Flores et al may be unreliable. But it may in fact be inappropriate to directly compare other studies' TCu 380A data, including that of Sivin and Stern, to Otero-Flores et al's data. Study design as well as participants' ages, gravidity/parity, environments and reported use duration were not the same. Otero-Flores et al participants were younger (≤30 years), exclusively nulligravid, 'highly educated' and based in a Mexico city with free access to healthcare in the millenial era, with the study being single-(patient) blinded. This contrasts with most studies involving the TCu 380A or similar IUDs where participants were more likely to be aged 30 or older, parous, with unspecified educational attainment. The Sivin and Stern study population were living and accessing healthcare (which was not stated to have been free) across the United States in the late 1970s (over two decades earlier than the Otero-Flores study, and not long after the Dalkon Shield era), with the study being double-blinded. Other explanations for disparity could be that modern younger nulligravids may be less tolerant of IUD unwanted effects, and that some contraceptive research may be less likely to acknowledge participants' reasons and wishes for early IUD discontinuation.[45]

The TCu 200 IUD was ≥33mm in width and/or height so perhaps larger than a standard-sized TCu 380A.[46] IUD size may contribute to pain, which may explain TCu 200's lower continuation rates compared to the TCu 380A. However the TCu 300, of same design and size as the TCu 200,[43] unexpectedly had a higher continuation rate than the TCu 200. This is because higher copper content has been associated with more bleeding which contributes to early discontinuation.[47] The TCu 300 data was limited to two studies that both had total MMAT scores of 7,[41, 43] whereas the TCu 200 data had been obtained from seven studies with MMAT scores of 7,[33, 34, 37, 41] 6,[35] and 5[39] respectively.

Strengths and Limitations

This is the first systematic review to explore IUD types in younger aged nulliparous women. It has included all observational studies that provided information on IUD continuation or reasons for discontinuation in this user group. Non-restriction to RCTs may be considered a limitation, but a realist approach of expanding the inclusion criteria where RCT evidence is lacking could be commendable and more representative of routine practice. Using the MMAT, the quality of reviewed and included studies in this systematic review was good overall.

Articles for inclusion were unfortunately limited to publications in the English language. The absence of studies on IUDs currently available in the UK solely involving women aged under 30 warranted a deviation from the protocol to include all ages up to 30 years for the TCu 380A data and meta-analysis. Many studies did not report all the required information hence some included studies had missing information (Table 3). Most studies did not differentiate between nulligravid and nulliparous participants, while some reports e.g. Sivin and Stern (1979) were of a combination of individual studies [42].

Relevance of Findings

IUD use in young and nulliparous women has been established to be safe, effective and acceptable.[48-50] It is recommended that women are provided the most appropriate IUD types for their uterine cavity size, with their uterine cavity width rather than length influencing IUD type choice.[25, 51-53] This systematic review emphasises this provision recommendation warrants further research and suggests IUD types for younger aged nulliparous women.

Recommendations

Strengthening evidence for contraceptive choice and continuation is needed to improve sexual health in younger aged women. Prospective observational studies that include various IUD designs and types, and detailed reporting of users' experiences could facilitate a better understanding of early IUD discontinuation and reasons for discontinuation based on IUD types. Studies designed to overcome the challenges of recruiting large numbers from varied demographic backgrounds, significant loss to follow up, and time or funding constraints are also likely to yield data widely applicable to IUC provision in and outside the UK.

CONCLUSION

Research is lacking on outcomes with the IUD types currently in use by younger aged nulliparous women in the UK. Available evidence estimates a continuation rate of 81% at 12 months for the recommended standard-sized TCu 380A IUD in these women. More studies are needed to better estimate continuation rates for smaller-sized and flexible IUDs which may be higher in this user group. This in turn will help to improve sexual health in younger aged women.

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COMPETING INTERESTS STATEMENT

The authors report no conflict of interest.

REPORTING STATEMENT CHECKLIST

See supplementary material 1.

DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

HA: research idea, study design, protocol, searches, first reviewer, data summary, writing - original draft, funding application for open access publishing, project administration; AJ: second reviewer, supervision, writing – review and editing, project administration; PB: searches, writing – review and editing; MM: meta-analysis, writing – original draft, review and editing; JR: contributed to research idea, study design, protocol, funding applications, and project administration, as well as supervision and writing – review and editing. All authors approved the final version.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 6-7 Supplementary material
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 6-7 Supplementary material
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6-7 Supplementary material
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7 Supplementary material
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7 Supplementary material
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 6-7 Supplementary material
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 6-7 Supplementary material
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7 Supplementary material
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-	Pages 6-7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		regression).	Supplementary material
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 6-7 Supplementary material
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 6-7 Supplementary material
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 6-7 Supplementary material
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 7-11 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 7-8 Supplementary material
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 11, 16-7 Table 3 Figures 2 – 6 Supplementary material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 16-7 Table 3 Figures 2–6 Supplementary material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 16-7 Figures 2–6 Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 16-7 Figures 2–6 Supplementary material
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 16-7 Figures 2–6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 17
	23b	Discuss any limitations of the evidence included in the review.	Page 18-9
	23c	Discuss any limitations of the review processes used.	Page 18-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5 Supplementary material
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplementary material
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 20
Competing interests	26	Declare any competing interests of review authors.	Page 20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Copper intrauterine contraception discontinuation in nulliparous and young women

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin

Citation

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin. Copper intrauterine contraception discontinuation in nulliparous and young women. PROSPERO 2019 CRD42019120969 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019120969

Review question

Which copper intrauterine devices are associated with higher discontinuation rates in young and nulliparous women?

Searches

Databases [including the Cochrane Library, the Database of Abstracts and Reviews of Effects (DARE), MEDLINE (Ovid), Excerpta Medica Database (EMBASE), Turning Research into Practice (TRIP) database and National Electronic Library of Health] and relevant websites [including Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, Medical Defence Unions, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar] will be searched using MeSH terms combined with key words for relevant articles published from 1966 to date. Reference lists of relevant articles will also be searched to identify more articles. The full texts of relevant articles will be screened, duplicates excluded and then data from selected articles included in the review.

Randomised controlled trials (RCTs) involving copper intrauterine devices (IUDs) available or comparable to those in the UK published in English will be included. Other studies that report on the main outcome (observational and qualitative studies) will be included and/or summarised if the number of RCTs eligible for inclusion are too few to answer the review question.

Key words

Copper intrauterine device related: copper intrauterine device, copper intrauterine contraceptive device, copper intrauterine contraception, copper coil, IUD

Nulliparous related: nulliparous, nulligravid, never pregnant, never delivered

Young women related: young women, adolescent, aged under, teenage

Types of study to be included

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved copper intrauterine devices available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over, or that involved copper intrauterine devices not available, or not of the same design and size to those available, in the UK.

Condition or domain being studied

Copper intrauterine contraception in nulliparous and young women

Participants/population

Women who are nulliparous and aged under 30

Intervention(s), exposure(s)

Copper intrauterine devices available or comparable to those in the UK

Comparator(s)/control

Any IUD, other contraceptive or no contraception where applicable

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Context

Copper intrauterine devices (IUDs) are of various shapes, sizes, copper surface area and copper distribution on the frame of the device. There are many types of IUDs available in the UK but none shown to be associated with better outcomes in nulliparous and young women. The identification and use of those IUDs associated with less discontinuation could improve outcomes including satisfaction and continuation rates of intrauterine contraception in nulliparous and younger women.

Main outcome(s)

Copper intrauterine contraception discontinuation rates in nulliparous and young women based on type of IUD

Timing and effect measures

Additional outcome(s)

Reasons for IUD discontinuation

Timing and effect measures

Data extraction (selection and coding)

The abstracts of published articles obtained from the literature and websites searches will be reviewed by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. All retrieved full texts of published articles will be reviewed to agree which studies to include in the systematic review, with disagreements resolved by the third author. All retrieved articles to be included in the systematic review will undergo a quality assessment using a risk of bias tool applicable to the type of study.

Main data to be extracted:

type of copper intrauterine device (IUD)

age of women

gravidity/parity of women

place/time of IUD insertion

IUD discontinuation rate(s)

reason(s) for IUD discontinuation

Risk of bias (quality) assessment

All retrieved articles to be included in the systematic review will undergo a quality assessment. One author will complete the inclusion criteria checklist while the second author will review the checklist, with disagreements resolved by the third author/consensus. Retrieved articles with a high risk of bias will be excluded from the systematic review.

Strategy for data synthesis

Data from the included studies will be extracted using a standardised form by one author while the second author will check these. Disagreements will be resolved by a further review of the study with the third author and consensus. One author will enter the extracted data into Review Manager (RevMan®) Software while the second author will again check these for accuracy. It is planned that aggregate data will be used. However, individual data on the intervention and population of interest (IUDs in nulliparous and young women aged under 30) will be extracted where studies have reported on this subgroup their outcomes in conjunction with other population subgroups or study outcomes.
A quantitative synthesis is planned based on the expected homogeneity of the data to be obtained for the main outcome to be studied. This homogeneous data will be combined for meta-analysis. Heterogeneous

data, some of which is expected to be obtained on the additional outcome, will be narratively synthesised.

Analysis of subgroups or subsets
IUDs of same size and design will be grouped and discontinuation rates presented based on IUD type.

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Anticipated or actual start date
28 January 2019

Anticipated completion date
31 January 2020

Funding sources/sponsors
Nil

Conflicts of interest

Language
English

Country
England

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Contraception; Copper; Female; Humans; Intrauterine Devices; Parity; Pregnancy

Date of registration in PROSPERO
07 February 2019

Date of publication of this version
07 February 2019

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

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Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

07 February 2019

TCu 380A continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(81.60% (95% CI 76.52-86.21%))**
Excluding Abraham et al. (<20)	82.04% (95% CI 76.48-87.04%)
Excluding Abraham et al. (20-25)	78.01% (95% CI 66.60-87.74%)
Excluding Hall and Kutler (18-30)	81.83% (95% CI 76.66-86.49%)
Subgroup 2 (Nulliparous women of any age)	**(80.97% (95% CI 76.04-85.48%))**
Excluding Abraham et al. (>25)	81.99% (95% CI 79.19-84.63%)
Excluding Akintomide et al. (15-37)	81.94% (95% CI 79.41-84.34%)
Excluding Roy et al. (14-33)	80.12% (95% CI 73.92-85.70%)
Overall effect size (all studies)	**(81.93% (95% CI 79.66-84.09%))**
Excluding Abraham et al. (<20)	81.84% (95% CI 79.13-84.40%)
Excluding Abraham et al. (20-25)	81.44% (95% CI 78.16-84.53%)
Excluding Hall and Kutler (18-30)	81.87% (95% CI 79.60-84.03%)
Excluding Abraham et al. (>25)	81.57% (95% CI 78.38-84.58%)
Excluding Akintomide et al. (15-37)	82.14% (95% CI 79.87-84.31%)
Excluding Roy et al. (14-33)	80.92% (95% CI 76.93-84.64%)

TCu 200 continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(73.03% (95% CI 67.63-78.10%))**
Excluding Lewit (15-19)	75.26% (95% CI 73.90-76.59%)
Excluding Lewit (20-24)	73.33% (95% CI 71.62-75.00%)
Excluding Lewit (25-29)	71.78% (95% CI 70.30-73.24%)
Subgroup 2 (Nulliparous women of any age)	**(76.51% (95% CI 72.67-80.14%))**
Excluding Roy et al. (14-33)	76.83% (95% CI 72.49-80.91%)
Excluding Luukkainen et al. (19-35)	76.53% (95% CI 71.86-80.91%)
Excluding Larsen et al. (15-44)	76.85% (95% CI 72.79-80.67%)
Excluding Ostergard and Gunning (18-34)	76.84% (95% CI 72.76-80.69%)
Excluding Lewit (30-34)	75.59% (95% CI 71.42-79.54%)
Excluding Lewit (35-49)	75.20% (95% CI 71.98-78.29%)
Excluding Liedholm and Sioberg (14-40)	77.32% (95% CI 73.40-81.01%)
Excluding Mishell et al. (14-33)	76.84% (95% CI 72.51-80.91%)
Overall effect size (all studies)	**(75.44% (95% CI 72.32-78.43%))**
Excluding Lewit (15-19)	76.43% (95% CI 73.71-79.04%)
Excluding Lewit (20-24)	75.59% (95% CI 71.81-79.17%)
Excluding Lewit (25-29)	76.16% (95% CI 71-60-78.56%)
Excluding Roy et al. (14-33)	75.56% (95% CI 72.16-78.81%)
Excluding Luukkainen et al. (19-35)	75.38% (95% CI 71.89-78.72%)
Excluding Larsen et al. (15-44)	75.60% (95% CI 72.34-78.70%)
Excluding Ostergard and Gunning (18-34)	75.59% (95% CI 72.33-78.71%)
Excluding Lewit (30-34)	74.72% (95% CI 71.59-77.73%)

Excluding Lewit (35-49)	74.37% (95% CI 71.53-77.10%)
Excluding Liedholm and Sioberg (14-40)	75.87% (95% CI 72.61-78.98%)
Excluding Mishell et al. (14-33)	75.56% (95% CI 72.16-78.81%)

TCu 200 discontinuation at 12 months due to pain/bleeding – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(7.05% (95% CI 5.59-8.65%))**
Excluding Lewit (15-19)	7.31% (95% CI 6.52-8.14%)
Excluding Lewit (20-24)	6.31% (95% CI 5.41-7.27%)
Excluding Lewit (25-29)	7.88% (95% CI 7.02-8.78%)
Subgroup 2 (Nulliparous women of any age)	**(12.77% (95% CI 8.48-17.78%))**
Excluding Roy et al. (14-33)	13.10% (95% CI 8.10-19.06%)
Excluding Luukkainen et al. (19-35)	11.02% (95% CI 8.41-13.92%)
Excluding Larsen et al. (15-44)	12.40% (95% CI 7.87-17.76%)
Excluding Ostergard and Gunning (18-34)	12.86% (95% CI 8.20-18.35%)
Excluding Lewit (30-34)	13.61% (95% CI 8.83-19.22%)
Excluding Lewit (35-49)	13.79% (95% CI 9.10-19.25%)
Excluding Liedholm and Sioberg (14-40)	12.08% (95% CI 7.56-17.45%)
Excluding Mishell et al. (14-33)	13.13% (95% CI 8.13-19.08%)
Overall effect size (all studies)	**(10.87% (95% CI 7.98-14.15%))**
Excluding Lewit (15-19)	11.37% (95% CI 8.08-15.12%)
Excluding Lewit (20-24)	11.23% (95% CI 7.70-15.32%)
Excluding Lewit (25-29)	11.52% (95% CI 8.34-15.14%)
Excluding Roy et al. (14-33)	10.90% (95% CI 7.77-14.47%)
Excluding Luukkainen et al. (19-35)	9.32% (95% CI 7.62-11.17%)
Excluding Larsen et al. (15-44)	10.51% (95% CI 7.58-13.86%)
Excluding Ostergard and Gunning (18-34)	10.78% (95% CI 7.77-14.20%)
Excluding Lewit (30-34)	11.23% (95% CI 8.01-14.92%)
Excluding Lewit (35-49)	11.34% (95% CI 8.17-14.94%)
Excluding Liedholm and Sioberg (14-40)	10.26% (95% CI 7.40-13.53%)
Excluding Mishell et al. (14-33)	10.92% (95% CI 7.78-14.50%)

TCu 200 discontinuation at 12 months due to expulsion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(10.52% (95% CI 7.17-14.41%))**
Excluding Lewit (15-19)	8.59% (95% CI 7.74-9.48%)
Excluding Lewit (20-24)	11.21% (95% CI 10.03-12.44%)
Excluding Lewit (25-29)	10.36% (95% CI 9.38-11.38%)
Subgroup 2 (Nulliparous women of any age)	**(4.93% (95% CI 2.93-7.39%))**
Excluding Roy et al. (14-33)	4.85% (95% CI 2.57-7.78%)
Excluding Luukkainen et al. (19-35)	4.17% (95% CI 2.68-5.96%)
Excluding Larsen et al. (15-44)	4.92% (95% CI 2.79-7.58%)
Excluding Ostergard and Gunning (18-34)	4.80% (95% CI 2.69-7.46%)
Excluding Lewit (30-34)	4.74% (95% CI 2.41-7.76%)
Excluding Lewit (35-49)	5.24% (95% CI 3.03-7.99%)
Excluding Liedholm and Sioberg (14-40)	5.84% (95% CI 3.95-8.07%)

Excluding Mishell et al. (14-33)	4.85% (95% CI 2.57-7.77%)
Overall effect size (all studies)	**(6.44% (95% CI 4.49-8.69%))**
Excluding Lewit (15-19)	5.76% (95% CI 4.14-7.61%)
Excluding Lewit (20-24)	6.16% (95% CI 3.87-8.93%)
Excluding Lewit (25-29)	6.16% (95% CI 3.96-8.79%)
Excluding Roy et al. (14-33)	6.55% (95% CI 4.47-8.99%)
Excluding Luukkainen et al. (19-35)	6.01% (95% CI 3.98-8.42%)
Excluding Larsen et al. (15-44)	6.54% (95% CI 4.51-8.91%)
Excluding Ostergard and Gunning (18-34)	6.46% (95% CI 4.43-8.83%)
Excluding Lewit (30-34)	6.47% (95% CI 4.36-8.95%)
Excluding Lewit (35-49)	6.87% (95% CI 4.87-9.18%)
Excluding Liedholm and Sioberg (14-40)	7.29% (95% CI 5.39-9.45%)
Excluding Mishell et al. (14-33)	6.55% (95% CI 4.47-8.99%)

TCu 200 discontinuation at 12 months due to pregnancy – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(2.19% (95% CI 1.47-3.05%))**
Excluding Lewit (15-19)	2.27% (95% CI 1.82-2.75%)
Excluding Lewit (20-24)	1.83% (95% CI 1.35-2.39%)
Excluding Lewit (25-29)	2.63% (95% CI 2.13-3.18%)
Subgroup 2 (Nulliparous women of any age)	**(1.15% (95% CI 0.54-1.95%))**
Excluding Roy et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Excluding Luukkainen et al. (19-35)	0.96% (95% CI 0.38-1.75%)
Excluding Larsen et al. (15-44)	1.18% (95% CI 0.53-2.05%)
Excluding Ostergard and Gunning (18-34)	1.31% (95% CI 0.65-2.16%)
Excluding Lewit (30-34)	1.35% (95% CI 0.70-2.18%)
Excluding Lewit (35-49)	1.31% (95% CI 0.62-2.20%)
Excluding Liedholm and Sioberg (14-40)	1.00% (95% CI 0.42-1.78%)
Excluding Mishell et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Overall effect size (all studies)	**(1.49% (95% CI 0.96-2.13%))**
Excluding Lewit (15-19)	1.39% (95% CI 0.81-2.09%)
Excluding Lewit (20-24)	1.34% (95% CI 0.83-1.94%)
Excluding Lewit (25-29)	1.48% (95% CI 0.87-2.22%)
Excluding Roy et al. (14-33)	1.46% (95% CI 0.89-2.16%)
Excluding Luukkainen et al. (19-35)	1.40% (95% CI 0.83-2.09%)
Excluding Larsen et al. (15-44)	1.53% (95% CI 0.98-2.19%)
Excluding Ostergard and Gunning (18-34)	1.62% (95% CI 1.07-2.26%)
Excluding Lewit (30-34)	1.69% (95% CI 1.18-2.29%)
Excluding Lewit (35-49)	1.64% (95% CI 1.10-2.28%)
Excluding Liedholm and Sioberg (14-40)	1.41% (95% CI 0.88-2.06%)
Excluding Mishell et al. (14-33)	1.46% (95% CI 0.89-2.16%)

Table – Characteristics of studies excluded following full text assessment

Study / Authors	Year	Country	Study Design	Study Objectives	Reasons for Exclusion
Akintomide et al[5]	2021	Austria, Finland, Germany, Poland, Sweden, UK	Prospective cohort	Secondary analysis of continuation, unwanted effects and cost consequences at 1 year in IUD users ≤30 in the European Active Surveillance Study for Intrauterine Devices	Undifferentiable results - IUD type categories based on IUD characteristics rather than brand or name of IUD
Garbers et al[16]	2013	USA	Retrospective records review	Prevalence and predictors of IUD discontinuation at 6 months in 306 Cu T380A users	Undifferentiable results; varied duration; 23 excluded from continuation analysis
Goldstuck[17]	1980	UK	Prospective cohort (selected)	Clinical evaluation of the combined multiload copper 250-mini IUD in selected nulliparous women	Undifferentiable results; disparity between data in tables and text
Hindle[23]	1978	Unable to confirm		Clinical evaluation and follow-up on 3,829 IUD procedures	Full text unobtainable
Lete et al[18]	1998	Spain	Prospective cross-sectional	Evaluation of IUD use in nulliparous women compared to parous women over a 12-year period	Data reported as incidence of events rather than rates
Ogedengbe et al[19]	1991	Nigeria	Prospective cohort	A comparison efficacy and discontinuation at 1 year of multiload and copper-T IUDs sequentially assigned to users	Parity of participants not detailed (mean parity 4); only one nulliparous participant
Patnaik[24]	2003	India	Unable to confirm	Uptake, satisfaction, retention and reasons for discontinuation of the copper T IUD	Full text unobtainable
Petersen et al[25]	1991	Unable to confirm	RCT – double blind	Significance of endometrial cavity length in the clinical performance of IUDs in nulligravidae	Full text unobtainable
Phillips et al[20]	2017	USA	Retrospective records review	Comparison of continuation and performance of levonorgestrel and copper intrauterine devices over 5 years	Undifferentiable results
Sivin and Tatum[21]	1981	USA	Prospective cohort	Clinical performance of the TCu 380A IUD over 4 years	Undifferentiable results
Teal et al[22]	2015	USA	Retrospective records review	Evaluation of the success and safety of intrauterine device (IUD) placement in adolescents based on age and parity	Undifferentiable results

References

5. Akintomide H, Brima N, Mansour DJ, et al, Copper IUD continuation, unwanted effects and cost consequences at 1 year in users aged under 30 – a secondary analysis of the EURAS-IUD study. The European Journal of Contraception & Reproductive Health Care, 2021. 26(3): p. 175-183.

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Supplementary material – Doi and forest plots

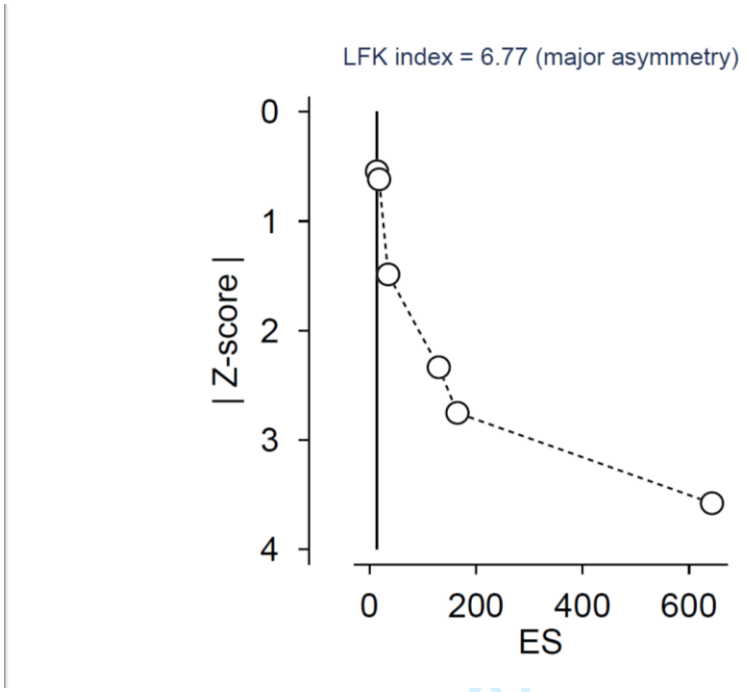

Figure 1 - Doi plot for TCu 380A continuation at 12 months

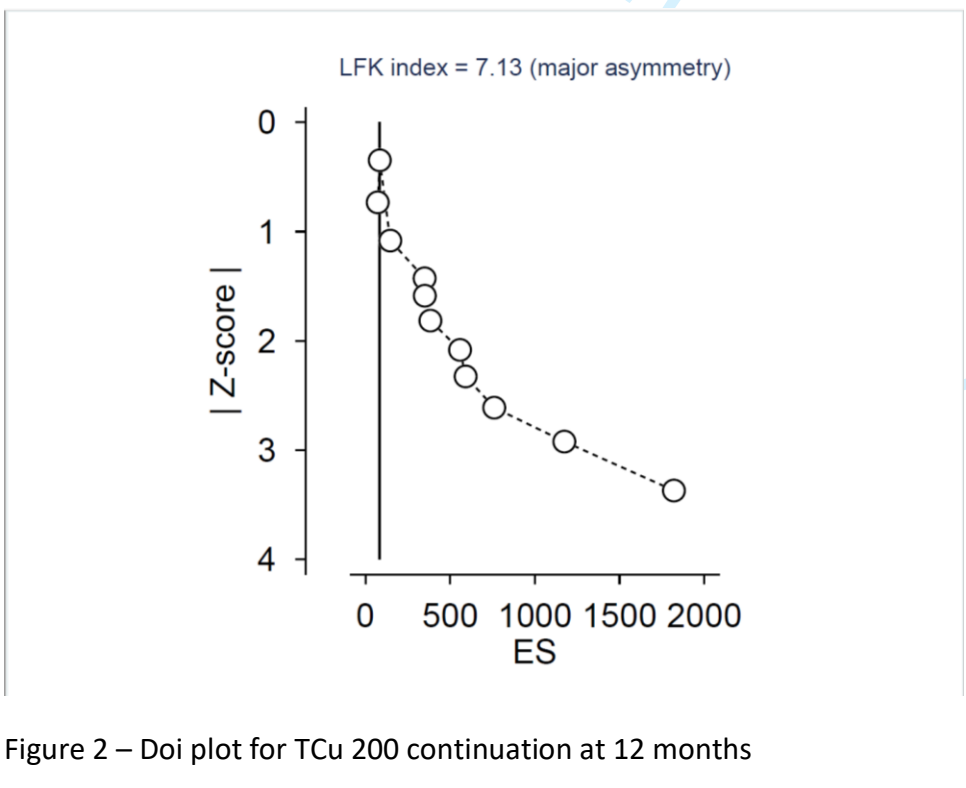

Figure 2 – Doi plot for TCu 200 continuation at 12 months

Supplementary material – Doi and forest plots

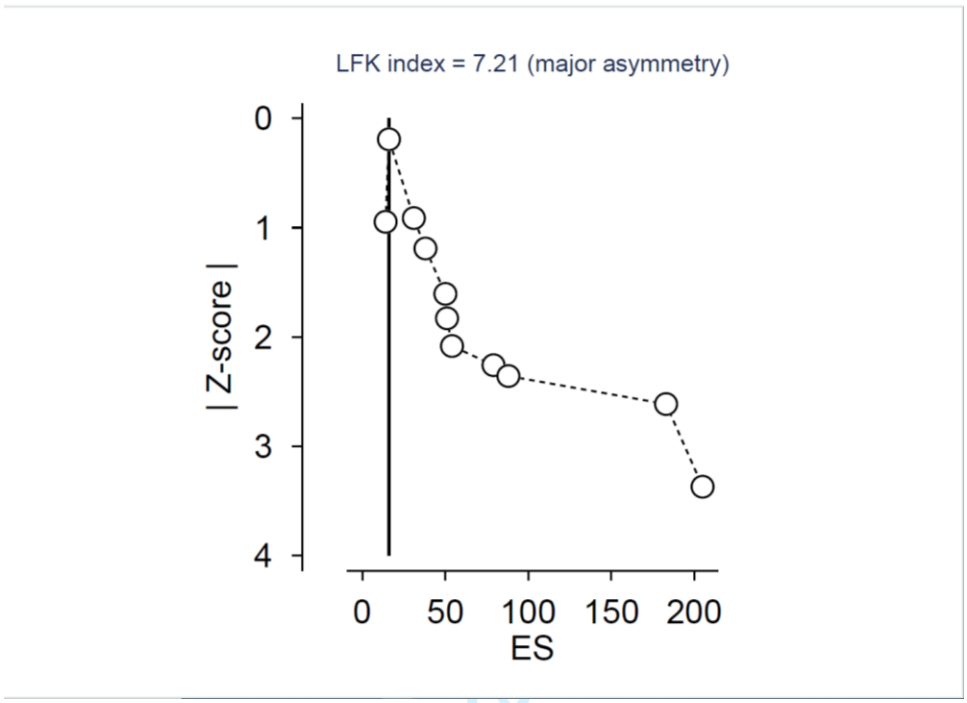

Figure 3 – Doi plot for TCu 200 discontinuation at 12 months due to bleeding/pain

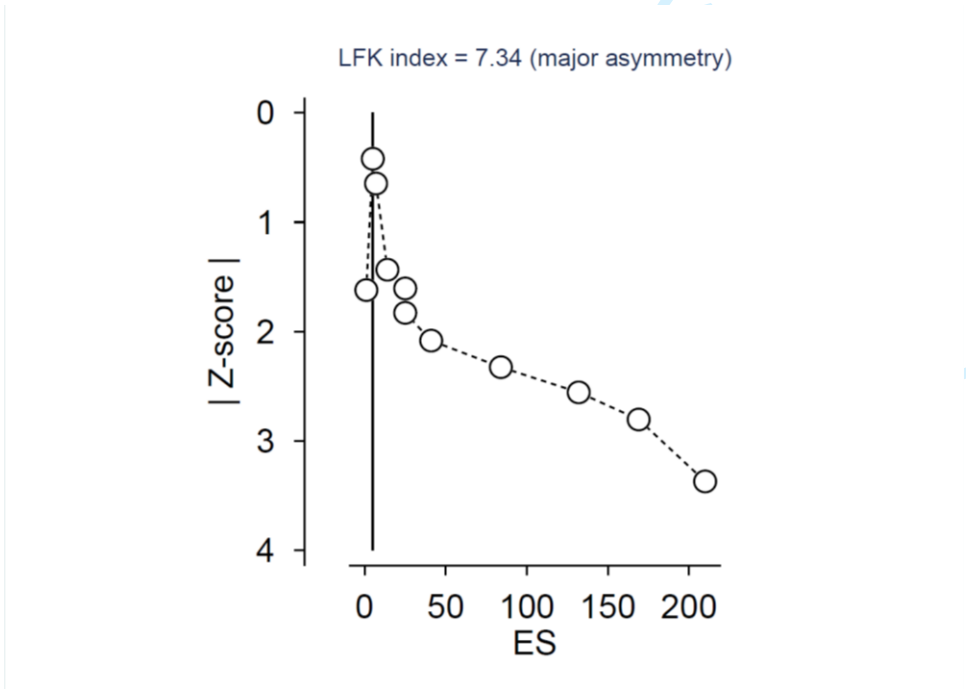

Figure 4 – Doi plot for TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – Doi and forest plots

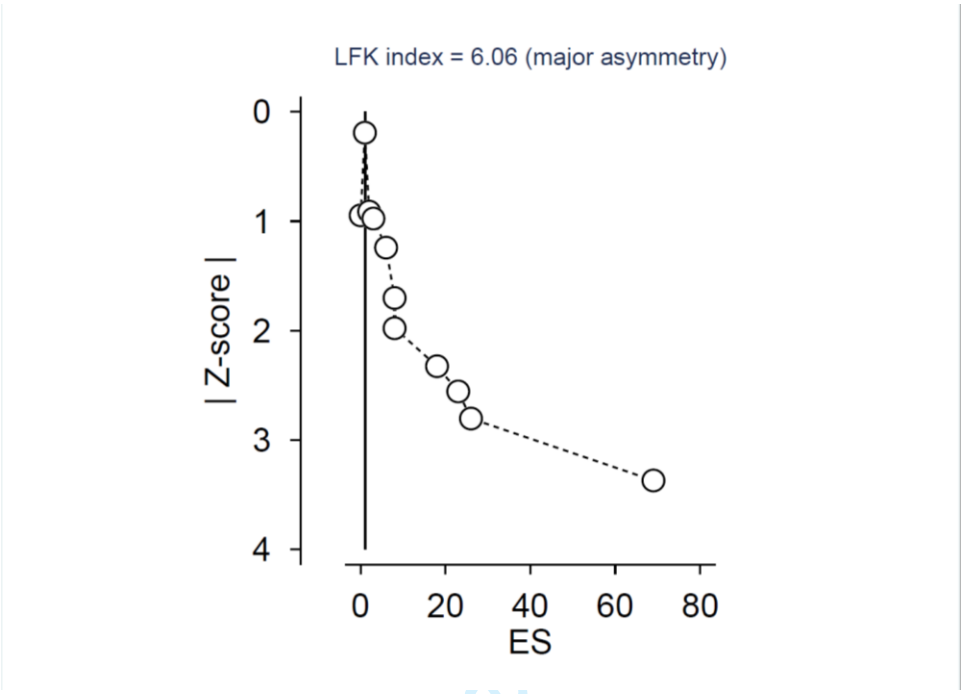

Figure 5 – Doi plot for TCu 200 discontinuation due to pregnancy

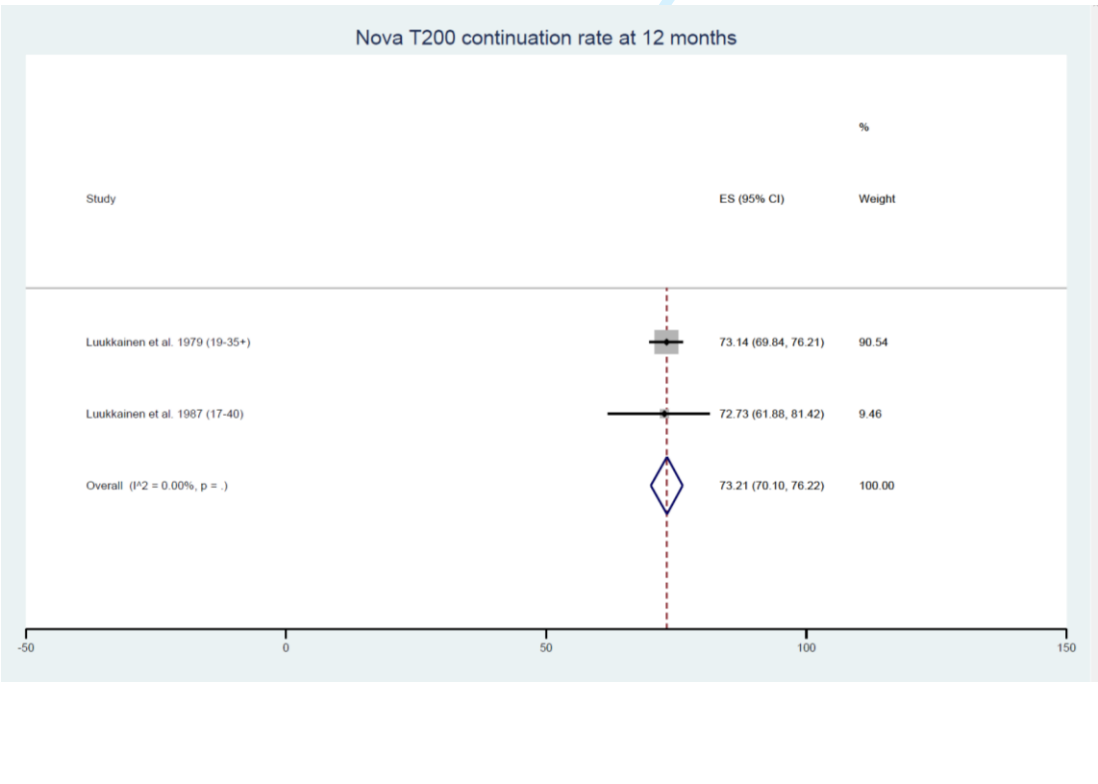

Figure 6 – Forest plot for Nova T200 continuation at 12 months

BMJ Open

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on IUD type

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-060606.R1
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TITLE PAGE

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on IUD type

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ABSTRACT

Objectives

No copper intrauterine device (IUD) type is known to better suit young nulliparous women who tend to experience higher rates of IUD discontinuation compared to their older parous counterparts. A systematic review to determine which IUDs have higher continuation rates in young nulliparous women was undertaken.

Design

Systematic review and meta-analyses of available evidence based on IUD type.

Data sources

AMED, BNI, CINAHL, DARE, EMBASE, EMCARE, HMIC, MEDLINE, PsychINFO, PubMed, TRIP, the Cochrane Library electronic databases; the Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar websites.

Eligibility criteria

All studies on IUDs currently available in the UK or comparable (same design and size) to those available in the UK involving nulliparous women of any age including those aged under 30.

Data extraction and synthesis

Independently extracted data were assessed as low risk of bias using the Mixed Methods Appraisal Tool. Random effects meta-analyses of proportions were performed where data including subgroups were amenable to quantitative synthesis. Heterogeneity was reported using the I^2 statistic and sensitivity analyses were also performed.

Results

Nineteen studies involving 13,045 nulliparous women were included. The highest continuation rates were reported with smaller-sized IUDs - TCu 380A Nul (91.3%), Multiload Cu 375 sl (89%), and Mini TT380 slimline (86.8%). The standard-sized Cu T380A and IUDs with rigid arms (Cu T or TCu) had higher discontinuation related to bleeding/pain and expulsion compared to smaller IUDs or those with flexible arms (Multiload, Nova T).

Conclusions

Evidence for IUD use in young nulliparous women based on IUD type remains limited. Smaller-sized IUD types appear better suited to this group of IUD users however more research is needed.

PROSPERO registration number CRD42019120969.

SHORT TITLE: Review of IUD continuation rates in young nulliparous women

KEY WORDS: IUD, continuation, discontinuation, reasons, young, nulliparous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first reported systematic review exploring IUD types in young nulliparous women
- A wide range of data sources unrestricted to randomised controlled trials was reviewed – an approach more representative of the real world
- Articles for inclusion were limited to publications in the English language
- Some data were obtained by calculation and measurements of graphs or figures where this was not numerically specified in reports
- Most studies did not differentiate between nulligravid and nulliparous participants

REPORTING STATEMENT CHECKLIST

See supplementary material 1

MAIN TEXT: (4366 words)

INTRODUCTION

The highest rates of unintended pregnancy and terminations of pregnancy, which contribute to poor sexual health, are in women aged 20-24 followed by those aged 25-29.[1] Increasing uptake of long-acting reversible contraceptives (LARC) like copper intrauterine contraception in these women is yet to yield a proportional reduction in pregnancy terminations, attributable to their higher LARC discontinuation rates.[2]

Copper intrauterine contraception is the LARC with the greatest number of brands, with 21 copper intrauterine devices (IUDs) available in the UK.[3] IUDs are of various shapes, sizes, total copper surface area and copper distribution on the IUD frame. They have changed little over the last 40 years. No IUD type has been shown to be associated with better outcomes regarding continuation or unwanted effects that lead to early IUD discontinuation. Early IUD discontinuation excludes discontinuation due to IUD user choice alone or the wish to conceive. IUD continuation rates tend to be surrogate for IUD satisfaction and/or acceptability. Studies have shown IUD continuation to be lower with unfavourable outcomes related to unwanted effects in adolescents and women in their 20s compared to their older counterparts, as well as in nulliparous compared to parous women.[4-8]

Previous systematic reviews and guidance suggest that IUD size and shape may be a factor in discontinuation and have recommended future research investigate which IUD types are associated with less pain, bleeding and discontinuation.[7, 9-11] The identification and use of those IUDs with higher continuation and fewer unwanted effects could improve outcomes including IUD satisfaction and continuation rates in young nulliparous women.

A systematic review and meta-analysis was therefore undertaken to investigate continuation rates and reasons for discontinuation of IUDs currently available or comparable to those currently in use in the UK based on IUD type involving women aged under 30.

OBJECTIVES

To determine which currently available IUDs have higher continuation rates in nulliparous women aged under 30 by systematically reviewing published studies. Discontinuation rates and reasons for discontinuation were secondary outcomes.

METHODS

An appraisal of previous systematic reviews including publications by the Cochrane Collaboration Fertility Regulation Group, Faculty of Sexual and Reproductive Healthcare (FSRH) and National Institute for Health and Care Excellence (NICE) was performed. A search strategy was developed in conjunction with an Electronic Services Librarian. These informed the design of this systematic review and its protocol.

This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline. Its protocol was registered on the International Prospective Register of Systematic Reviews database (PROSPERO; CRD42019120969, see supplementary material 2).[12] The protocol included an approach to consider other studies besides randomised controlled trials (RCTs) that report on IUD continuation if the RCTs determined eligible for inclusion in the systematic review were too few to address the review question.

Selection criteria

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved IUDs available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over 30, that involved IUDs not available, or not of the same design and size to those available, in the UK.

Where studies on IUDs currently available in the UK or only involving nulliparous women aged under 30 were lacking, studies with IUDs comparable in shape, size, total copper surface area or distribution on the IUD frame to those currently available in the UK, as well as with nulliparous women of all ages where those aged under 30 were involved, are included in this review.

Search Strategy

Nine electronic databases - the Allied and Complementary Medicine (AMED), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Nursing and Allied Health Professionals Database (EMCARE), Health Management Information Consortium (HMIC), General Medical Database (MEDLINE), Psychology and Allied Fields (PsychINFO), and PubMed – were searched using search terms (copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab from database inception to 7 February 2021 (updated to 11 May 2022). The following additional sources were searched using the term 'Copper intrauterine': the Cochrane Library, Database of Abstracts and Reviews of Effects (DARE), Turning Research into Practice (TRIP) database, National Electronic Library of Health (merged with MEDLINE), Bandolier, Medicines and Healthcare products Regulatory Agency, FSRH, Royal College of Obstetricians and Gynaecologists, Department of Health, NICE, Scottish Intercollegiate Guidelines, and World Health Organisation websites. A Google Scholar search was also undertaken using the term 'Copper intrauterine device young nulliparous'. The full search strategy is provided as a supplementary file (supplementary material 3).

Relevant articles published in English were identified by two authors and these exported into an Endnote library upon completion of searches. Following de-duplication, the relevant articles obtained from searches were exported to Rayyan, a web app for systematic reviews (rayyan.ai). In Rayyan, further de-duplication yielded unique entries of which abstracts, and then full texts, were screened independently by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. Additional citation screening of reference lists of both included and excluded studies was performed. Screening was initially done in batches of 20, then later increased to 50. Agreements were obtained between the first two authors and did not require a third review. Selected articles were RCTs and observational studies published in English involving IUDs available or comparable to those in the UK involving nulliparous participants aged under 30.

Quality Assessment and Data Summary

All articles selected for inclusion in the systematic review underwent a quality assessment using the Mixed Methods Appraisal Tool version 2018 (MMAT).[13] The MMAT risk of bias tool was chosen because it was applicable to all the study types of articles selected for inclusion. The highest possible total MMAT score conforming with best quality was seven, while the lowest possible score for poor quality was zero. Included articles were initially quality assessed by the two authors separately and then agreement reached.

Data extracted from articles included IUD type, study location(s) and year of publication, age of women, gravidity/parity of women, IUD continuation and discontinuation rates, and reasons for IUD discontinuation. Where a rate was not specified but could be reliably calculated, this was done to one decimal place. If a continuation rate was not specified, this was obtained by subtracting the discontinuation rate from 100, or adding all stated rates for reasons for discontinuation where these were mutually exclusive and subtracting from 100, if the report suggested such a calculation to be valid. If a discontinuation rate was not specified, this was obtained by subtracting a stated

continuation rate from 100, or by adding all stated rates for reasons for discontinuation where these were mutually exclusive, if the report suggested such a calculation was valid. Gross rates (obtained after excluding participants lost to follow up or removals to conceive) were used, except where only net cumulative rates were reported. Measurements were performed to obtain data from published graphs or figures where rates had been reported in this format but not numerically specified.

An Excel data collection form was developed, piloted with three articles selected for inclusion by one author, then revised and amended by the second author before proceeding to data extraction. Data from the 19 selected articles included in the review were extracted by one author unto the Excel spreadsheet and checked by the second author.

Data Analysis

Where available data were amenable to quantitative synthesis, random effects meta-analyses of proportions were performed using the metaprop suite of commands on STATA 16. Variances were stabilised using the Freeman-Tukey double arcsine transformation. This approach provides better approximation and results between 0% and 100% when synthesising proportions from small samples and multiple studies in meta-analyses.[14] Where possible, subgroup analysis was performed to examine differences between nulliparous women aged ≤30 years and nulliparous women of any age. Statistical heterogeneity was reported using the I^2 statistic, since random effects meta-analyses was being performed. The I^2 value describes the percentage of the variability in effect estimates that is due to statistical heterogeneity (reflecting methodological diversity among the included studies) as opposed to chance. Conventionally, while an I^2 value <40% may not be significant, a value >50% may represent substantial heterogeneity and a value >75% may indicate considerable heterogeneity.[15] The effect of removing individual studies on the overall effect size was explored in sensitivity analyses (supplementary material 4). Publication bias was examined by producing Doi plots and generating LFK index values, considered a more appropriate measure of publication bias than funnel plots/Egger's test when performing meta-analyses of proportions.[16]

Patient and Public Involvement

The FSRH is the UK organisation committed to meeting the highest SRH standards, ensuring improvements in population SRH and supporting SRH professionals. The FSRH's Contraceptive Priority Setting Partnership in liaison with the James Lind Alliance yielded over 700 responses from patients, practitioners and the public that identified: 'Which interventions increase uptake and continuation of effective contraception including long-acting methods…?' as the top SRH research priority.[17] This influenced the research aims. IUD users attending a sexual health clinic over a four-week period were consulted about improving access to and use of intrauterine contraception. Their suggestions, which included studying women's experiences with IUDs, were used in developing the research question, aim, and study design. The Consumer Panel of the North East Research Design Service was also consulted and the proposed research presented to them. The research plan was modified in line with their feedback.

Ethics Approval Statement

This study does not involve human participants and does not involve animal subjects. It was therefore exempt from Research Ethics Committee review.

RESULTS

Only one study, a prospective (non-RCT) cohort, provided information on an IUD available in the UK solely involving nulliparous users aged under 30.[18] This was inadequate to address the review question. As per the systematic review protocol, other studies on IUDs currently available in the UK or IUDs comparable (same design and size) to those available in the UK (Box 1) involving nulliparous women of all ages (so not limited to those aged under 30) were also screened.

Box 1 – Characteristics of IUDs in included studies

IUD brand / name	Copper (mm^2)	shape / design	width (mm)	arms' flexibility
Currently available in the UK				
Cu T380A / TCu 380A / TT380 Slimline	380	T with arm bands	>30	No
TCu 380A Nul / Mini TT380 slimline	380	T with arm bands	23.2	No
Multiload Cu 375	375	Ω	16 – 20.5	Yes, flex down
Nova T 380	380	T without arm bands	>30	Yes, flex up
Comparable to those available in the UK				
Nova T 200	200	T without arm bands	≥30	Yes, flex up
TCu 300	300	T without arm bands	>30	No
Cu T200 / TCu 200	200	T without arm bands	>30	No
TCu 220C	220	T without arm bands	>30	No

Thirty records were obtained upon this expansion and their full texts assessed. Eleven records were excluded for lack of usable outcome data (n=8; [5, 19-25]) and their full texts unobtainable (n=3; [26-28]) (see supplementary material 5). A total of 19 studies on IUDs available or comparable to those available in the UK in nulliparous women were eventually obtained and included in the systematic review (Table 1).[18, 29-46] Figure 1 depicts a PRISMA flow diagram detailing the search and selection process.[47]

Table 1 – Characteristics of Included Studies

Study / Authors	Year	Country	Study Design	Study Objectives	IUDs in study	Quality (MMAT score)
Abraham et al [18]	2015	USA	Prospective cohort	Relationship among young age, nulliparity, and continuation of long-acting reversible contraceptives	Copper T380A	Good (7)
Akintomide et al [29]	2019	UK	Retrospective records review	Discontinuation rates and reasons for discontinuation at 1 year of the small-sized Mini TT380 Slimline IUD compared with the standard-sized TT380 Slimline	Mini TT380 slimline TT380 slimline	Good (6)
Allonen et al [30]	1980	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 2 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (6)
Elkhateeb et al [31]	2020	Egypt	Prospective cohort	Acceptability of IUD use in nulliparous women by both women and health care providers	Copper T380A	Good (7)
Fugere [32]	1990	Canada	Prospective cohort	Clinical performance of the Nova T200 IUD over 5 years	Nova T200	Good (7)
Hall and Kutler [33]	2016	USA	Prospective cohort	Experience and satisfaction of nulliparous intrauterine contraception users at 1, 6, 12 and 18 months	Copper T380A	Good (7)
Kaislasuo et al [34]	2015	Finland	Prospective cohort	Menstrual characteristics and ultrasonographic uterine cavity measurements predict bleeding and pain in nulligravid women using intrauterine contraception	Nova T380	Good (7)
Larsen et al [35]	1981	Denmark	RCT – patient blind	Comparison of clinical performances of Progestasert and Copper T200 at 12 months	Copper T200	Good (5)
Lewit [36]	1973	USA	Prospective cohort	Two years' experience of the Copper T200	Copper T200	Good (7)
Liedholm and Sjoberg [37]	1974	Sweden	Prospective cohort	Two years' experience with the Copper T200 and comparison between nulliparous and parous women	Copper T200	Good (7)
Luukkainen et al [38]	1979	Denmark, Finland Sweden	RCT – double blind	Experience and clinical performance of the Nova T200 and Copper T200 at 12 months	Nova T200 Copper T200	Good (6)
Luukkainen et al [39]	1987	Denmark, Finland, Hungary, Norway, Sweden	RCT – no blinding	Use-effectiveness and clinical performance of levonorgestrel- and copper-releasing intrauterine devices at 12 months	Nova T200	Good (6)
Mishell et al [40]	1973	USA	Prospective cohort	Continuation and clinical performance of TCu 200 in nulliparous women	Copper T200	Good (7)
Nygren et al [41]	1981	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 3 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (7)

Ostergard and Gunning [42]	1979	USA	RCT – blinding not stated	Continuation and clinical performances of Copper T200 and Dalkon Shield in nulligravid women at 12 months	Copper T200	Good (5)
Otero-Flores et al [43]	2003	Mexico	RCT – single (patient) blind	Comparison of clinical performance of three different IUDs in nulliparous women	Copper T380A Copper T380A Nul Multiload 375 sl	Good (6)
Roy et al [44]	1974	USA	Prospective cohort	Experience with three different IUD models in nulliparous women at 1 year	Copper T380A Copper T300 Copper T200	Good (7)
Sivin and Stern [45]	1979	USA	RCT – double blind	Experience of three different IUDs in nulliparous and parous women	Copper T380A Copper T220C Copper T200	Good (5)
Timonen et al [46]	1974	Finland	Prospective, single (patient) blind	Use-effectiveness of Copper T300 at 1 year	Copper T300	Good (7)

All included studies were generally of good quality (mean 6.42 [5-7]; see supplementary material 6 for quality and risk of bias assessments). The lowest MMAT score of five obtained was for three RCTs published in 1979 and 1981, possibly related to inadequate reporting.[35, 42, 45] Their reports did not confirm that randomisation had been appropriately performed, [35, 45] randomised groups were comparable at baseline, [42, 45] nor that outcome assessors were blinded to the intervention provided [35, 42].

Although the outcome data obtained were considered homogenous, studies' designs, participant ages and parity, and IUD types were not; making a quantitative synthesis of the outcome data in totality inappropriate. Results were therefore grouped into three to include studies involving: 1. IUD types currently available in the UK and only nulliparous women aged ≤30; 2. IUD types currently available in the UK and nulliparous women of all ages; 3. IUD types comparable to those available in the UK and nulliparous women of all ages. (Table 2) Estimated continuation rates at 12 months of IUD types from included studies obtained from data amenable to synthesis is reported in Table 3.

Table 2 – Summary of Findings

Study	IUD types (N[µ])	Age at insertion (y)	Study period	Continuation rates % (n)[CI]	Discontinuation rates % (n)	Removal for bleeding/pain % (n)	Expulsion % (n)	Pregnancy % (n)
Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30								
RCT								
Otero-Flores et al 2003 [43] [µ §]	TCu 380A (375) TCu 380A Nul (367) ML Cu 375 sl (374)	23.2±6.8 22.4±6.6 22.6±6.4	12 months	30.7 (115) 91.3 (335) 89.0 (333)	69.3 (260) 8.7 (32) 11.0 (41)	61.6 (231) 3.81 (14) 6.68 (25)	3.47 (13) 1.91 (7) 1.87 (7)	1.07 (4) 0.54 (2) 0.00 (0)
Non-RCT								
Abraham et al 2015 [18]	Cu T380A (201) Cu T380A (44) Cu T380A (201) Cu T380A (44)	20 - 25 <20 20 - 25 <20	12 months 24 months	82 [76-87] 79 [64-89] 73 [66-79] 64 [48-77]	ns ns	ns ns	ns ns	ns ns
Hall and Kutler 2016 [33]	Cu T 380A (21)	18 - 30	12 months	73.7 (14)	26.3 (5)	10.5 (2)	10.5 (2)	5.26 (1)
Studies of IUD types currently available in the UK involving nulliparous women of all ages								
RCTs								
Sivin and Stern 1979 [45][¶,a]	TCu 380A (2254) TCu 220C (1301) TCu 200 (4215)	<20 - 35+ <20 - 35+ <20 - 35+	2y	55.7 57.8 54.2	44.3 42.2 45.8	21.9 19.5 16.8	7.8 9.8 9.8	0.8 1.6 5.1
Non-RCTs								
Akintomide et al 2019 [29]	TT380 Slimline (27) Mini TT380 Slimline (53)	15 – 37 16 - 37	1y	66.7 (18) 86.8 (46)	33.3 (9) 13.2 (7)	ns ns	3.7 (1) 3.77 (2)	0 (0) 0 (0)
Elkhateeb et al 2020	TCu 380A (90)	16 - >30	6 months	94.4 (85)	5.6 (5)	ns	0 (0)	ns

[31]								
Kaislasuo et al 2015 [34]§	Nova T380 (42)	18 - 43	1y	83.3 (35)	16.7 (7)	ns	4.76 (2)	ns
Roy et al 1974 [44]	TCu 380A (785) TCu 300 (347) TCu 200 (472)	<14 - >33 15 - >33 <14 - >33	12 months	81.9 80.7 74.2	18.1 19.3 25.8	9.1 9.2 10.7	3.8 6.1 5.4	0.2 0.6 1.7
Studies of IUD types comparable to those available in the UK involving nulliparous women of all ages								
RCTs								
Luukkainen et al 1979 [38][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	12 months	ns ns	ns ns	15.3 23.4	6 10.8	0.53 2.3
Allonen et al 1980 [30][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	24 months	ns ns	ns ns	23.5 24	6.5 14	1.14 5.28
Nygren et al 1981 [41][a]	Nova T200 (ns) Cu T200 (ns)	<20 - >35	36 months	36.9 31.0	ns ns	28.3 (74) 28.2 (68)	10.3 (27) 10.7 (26)	1.5 (4) 6.5 (15)
Larsen et al 1981 [35][a]	Cu T200 (99)	15 - 44	12 months	73	27[α]	16	5	1
Luukkainen et al 1987 [39]	Nova T200 (77)	17 – 40	12 months	73.1	26.9[α]	10.4	9.2	0
Ostergard and Gunning 1979 [42]	TCu 200 (117) TCu 200 (115)	18 – 34	6 months 12 months	88.9 (104) 73.0 (84)	11.1 (13) 27.0 (31)	6.0 (7) 12.2 (14)	3.41 (4) 6.09 (7)	0 (0) 0 (0)
Non-RCTs								
Fugere 1990 [32]	Nova T200 (54)	17 - 42	24 months	ns	ns	17.2	1.9	0
Lewit 1973 [36]	TCu-200 (2099) Nulligravid subgroup: TCu-200 (1585)§ Age subgroups: TCu-200 (1130) TCu-200 (2468) TCu-200 (1513)	15-49 15-49 15 – 19 20 – 24 25 – 29	1y 1y 1y 1y 1y	73.3 75.9 67.3 73.8 77.6	26.7 24.1 32.7 26.2 22.4	9.4 9.6 7 8.3 5.8	10.7 8.7 15 8.5 8.7	1.3 0.8 2.3 2.8 1.5

	TCu-200 (683) TCu-200 (449)	30 – 34 35 - 49	1y 1y	81.7 85.2	18.3 14.8	7.9 6.8	6 3.1	0.4 0.3
Liedholm and Sjoberg 1974 [37]	T-Cu 200 (208) `	14 - 40	12 months 24 months	70.2 60.3	29.8 39.7	18.1 28	0.5 0.5	2.9 (6) 2.9 (6)
Mishell et al 1973 [40][a]	TCu 200 (471)	14-33	3 months 6 months 12 months	92.6 84.5 74.2	7.4 15.5 25.8	2.8 5.8 10.7	2.6 4.7 5.4	0.2 0.4 1.7
Timonen et al 1974 [46]	T Cu-300 (138)	<25 - 40+	12 months	84.7	15.3	7.2	1.6	1.6

RCT – randomised controlled trial; ns – not stated; μ - sample size or participants excluding those lost to follow up or removals to plan pregnancy; § - nulligravid women only; ¶ - a combination of double blind studies; α – not stated; obtained by subtraction of continuation rate from 100; a – net cumulative rates; b – data obtained from graphs or figures

Table 3 – Estimated continuation rates at 12 months of IUD types from included studies

IUD type	Nulliparous women aged <30	Nulliparous women of any age	Overall effect size (all studies)
TCu 380A[a]	81.60% (95% CI 76.52-86.21%)[b] ($I^{\wedge 2}$ = .%, p = .)	80.97% (95% CI 76.04-85.48%) ($I^{\wedge 2}$ = .%, p = .)	81.93% (95% CI 79.66-84.09%) ($I^{\wedge 2}$ = 0.00%, p = 0.47);
Smaller TCu 380A[c]	not applicable – only one study	91.02% (95% CI 88.01-93.64%) ($I^{\wedge 2}$ = 0.00%, p = .)	91.02% (95% CI 88.01- 93.64%) ($I^{\wedge 2}$ = 0.00%, p = .)
TCu 300	not applicable – no study	81.92% (95% CI 78.35-85.24%) ($I^{\wedge 2}$ = 0.00%, p = .)	81.92% (95% CI 78.35-85.24%) ($I^{\wedge 2}$ = 0.00%, p = .)
TCu 200	73.03% (95% CI 67.63-78.10%) ($I^{\wedge 2}$ = .%, p = .)	76.51% (95% CI 72.67-80.14%) ($I^{\wedge 2}$ = 82.97%, p = 0.00)	75.44% (95% CI 72.32-78.43%) ($I^{\wedge 2}$ = 89.17%, p = 0.00)
Nova T200	not applicable – no study	73.21% (95% CI 70.10-76.22%) ($I^{\wedge 2}$ = 0.00%, p = .)	73.21% (95% CI 70.10-76.22%) ($I^{\wedge 2}$ = 0.00%, p = .)

a – excludes Otero-Flores et al study data; b – includes women aged 30 from Hall and Kutler study data; c – TCu 380A Nul/Mini TT380 Slimline IUDs

Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30

Three studies - Abraham et al (2015), Hall and Kutler (2016) and Otero-Flores et al (2003) - reported on IUDs in women aged ≤30 involving the Copper T380A IUD (TCu 380A or Cu T380A).[18, 33, 43] The TCu 380A data obtained from Otero-Flores et al (2003) was an outlier, with 30.7% reported as continuation at 12 months[43]. This was much lower than for the other two studies with a pooled estimate of 81.60% (95% CI 76.52-86.21%).[18, 33] (Figure 2) When the Otero-Flores et al data were included in this TCu 380A meta-analysis, nulliparous women ≤30 years of age at 12 months had a continuation rate of 66.98% [95% CI 32.09-93.90%]. (Figure 3)

Continuation was also higher with age at 12 and 24 months when nulliparous TCu 380A IUD users aged <20 and 20 - 25 were compared (Table 2).[18]

Studies of IUD types currently available in the UK involving nulliparous women of all ages

Five studies reporting data pertaining to seven population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the TCu 380A IUD at 12 months post insertion.[18, 29, 33, 43, 44] The pooled estimated continuation rate of the Copper T380A IUD type in nulliparous women of all ages from four studies was 81.93% (95% CI 79.66-84.09%); overall I^2 = 0.00%, p = 0.47.[18, 29, 33, 44]. The estimated TCu 380A continuation rate was still good at 71.6% (95% CI 51.15-88.44%) when the Otero-Flores et al data was included. (Figure 3). Additionally, statistical heterogeneity using the I^2 statistic was found to be low/absent but was not statistically significant (I^2 = 0.00%, p = 0.47). Sensitivity analysis confirmed that the overall effect size was largely robust to the exclusion of individual studies (-1.01% to +0.21% change in effect size, see supplementary material 3). An LFK index value of 6.77 identified major Doi plot asymmetry consistent with publication bias (see supplementary material 7).

Individual studies showed the TCu 380A had higher discontinuation related to bleeding/pain and expulsion [33, 43, 45] when compared to IUDs of smaller size or those with flexible arms [29, 43](Table 2).

The highest continuation rates at 12 months were reported with smaller-sized IUDs - the Copper 380A Nul (TCu 380A Nul - 91.3%), Multiload Copper 375 sl (ML Cu 375 sl - 89%), and Mini TT380 slimline (86.8%)(Table 2). These data were obtained from only two studies whose participants were aged 15 to 37.[29, 43] Meta-analysis of continuation rate data on the TCu 380A Nul/Mini TT380 slimline IUD type gave a weighted average of 91.02% (95% CI 88.01-93.64%) (Figure 4). These smaller IUDs were also associated with the lowest rates of removals for bleeding/pain (3.80 – 6.68%) and expulsion (1.87 – 3.77%) reported in nulliparous women at 12 months (Table 2).

STUDIES of IUD types comparable to those in the UK involving nulliparous women of all ages

Two studies reporting data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T300 IUD (TCu 300) at 12 months post insertion [44, 46], reporting an overall effect size of 81.9% (95% CI 78.35-85.24%, see figure 5).

Seven studies reporting data pertaining to 11 population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T200 IUD (TCu 200 or Cu T200) at 12 months post insertion, with a weighted average of 75.44% (95% CI 72.32-78.43%, see figure 6).[35-37, 39, 40, 42, 44] These were also amenable to meta-analysis examining the proportion of women discontinuing the TCu 200 at 12 months post insertion due to bleeding and/or pain, expulsion and pregnancy (see supplementary material 8). For these meta-analyses, nulliparous women aged <30 years compared to nulliparous women of any age at 12 months were found to be less likely to continue to use the TCu 200 (73.03% [95% CI 67.63-78.10%] versus 76.51% [95% CI 72.67-80.14%]) and discontinue the TCu 200 due to bleeding and/or pain (7.05% [95% CI 5.59-8.65%] versus 12.77% [95% CI 8.48-17.78%]). Nulliparous women aged <30 years

compared to nulliparous women of any age at 12 months were however more likely to discontinue the TCu 200 due to expulsion (10.52% [95% CI 7.17-14.41%] versus 4.93% [95% CI 2.93-7.39%]) and pregnancy (2.19% [95% CI 1.47-3.05%] versus 1.15% [95% CI 0.54-1.95%]). Statistical heterogeneity using the I^2 statistic were all found to be substantial for overall TCu 200 continuation rates and discontinuation rates for bleeding/pain and expulsion - $I^{\wedge 2}$ = 89.17%, p = 0.00; $I^{\wedge 2}$ = 94.59%, p = 0.00; and $I^{\wedge 2}$ = 92.58%, p = 0.00) respectively (see figure 6 and supplementary material 8). Sensitivity analyses confirmed that the overall effect sizes were largely robust to the exclusion of individual studies. In all cases, their LFK index values identified major Doi plot asymmetry consistent with publication bias (see supplementary material 7).

Continuation was seen to progressively improve with age where Lewit (1973) reported rates in nulliparous TCu 200 users by age groups 15 – 19, 20 – 24, 25 – 29, 30 – 34, and 35 – 49.[36] (Table 2)

Two studies reported data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Nova T200 at 12 months post insertion,[38, 39] reporting a weighted average of 73.21% (95% CI 70.10-76.22%, see figure 7).

Studies also showed IUDs with flexible arms (Nova T, Multiload)[30, 38, 43] were associated with higher continuation and lower removal rates for bleeding/pain, expulsion and pregnancy where compared to IUDs with rigid arms (Cu T or TCu). (Table 2).

DISCUSSION

Findings and Interpretation

Evidence on IUDs currently used in nulliparous women aged under 30 is limited. These findings estimate the continuation rate for the recommended TCu 380A IUD [11] to be 81% at 12 months post insertion based on four studies involving young nulliparous women.[18, 29, 33, 44] This was the same estimate for the TCu 300 based on two studies.[44, 46] Smaller sized and flexible IUDs had higher continuation rates of 86-91% in this group of women based on two studies as well as fewer removals for bleeding/pain and expulsion compared to the TCu 380A or IUDs of same rigid design or size.[29, 43] Lower continuation rates of 75% and 73% were obtained for the TCu T200 and Nova T200 based on eight studies.[35-40, 42, 44]

The study by Otero-Flores et al was the only reported RCT at 12 months to solely involving IUDs currently used in the UK and nulliparous women aged ≤30.[43] Over a thousand nulliparous women aged 15 to 30 were randomised to receive three different IUDs - TCu 380A (width 32mm), TCu 380A Nul (width 23mm) and ML Cu 375 sl (width ≤20mm), the latter two of which were primarily designed for nulliparous women. The TCu 380A rates of discontinuation (69.3%) and bleeding/pain as reasons for discontinuation (61.6%) were significantly higher than for TCu 380A Nul (8.7% and 3.81%) and ML Cu 375 sl (11.0% and 6.68%), as well as significantly different from rates reported by other included studies involving the TCu 380A. This could be because the TCu 380A considerably differs in size from the TCu 380A Nul and ML Cu 375 sl IUDs, and Otero-Flores et al also exclusively involved nulligravid participants (as opposed to nulliparous).

Sivin and Stern (1979) was the only other RCT involving a TCu 380A that reported separately on nulliparous users.[45] However, their TCu 380A discontinuation and bleeding/pain rates, 44.3% and 21.9% respectively, were obtained at two years and their participants aged <20 to 35+.

The disparity in discontinuation rates reported by Otero-Flores et al [43] and Sivin and Stern [45], in addition to criticism for inaccuracies, have suggested that the findings by Otero-Flores et al may be unreliable. But it may in fact be inappropriate to directly compare other studies' TCu 380A data, including that of Sivin and Stern, to Otero-Flores et al's data. Study design as well as participants' ages, gravidity/parity, environments and reported use duration were not the same. Otero-Flores et al participants were younger (≤30 years), exclusively nulligravid, 'highly educated' and based in a Mexico city with free access to healthcare in the millenial era, with the study being single-(patient) blinded. This contrasts with most studies involving the TCu 380A or similar IUDs where participants were more likely to be aged 30 or older, parous, with unspecified educational attainment. The Sivin and Stern study population were living and accessing healthcare (which was not stated to have been free) across the United States in the late 1970s (over two decades earlier than the Otero-Flores study, and not long after the Dalkon Shield era), with the study being double-blinded. Other explanations for disparity could be that modern younger nulligravids may be less tolerant of IUD unwanted effects, and that some contraceptive research may be less likely to acknowledge participants' reasons and wishes for early IUD discontinuation.[48]

The TCu 200 IUD was ≥33mm in width and/or height so perhaps larger than a standard-sized TCu 380A.[49] IUD size may contribute to pain, which may explain TCu 200's lower continuation rates compared to the TCu 380A. However the TCu 300, of same design and size as the TCu 200,[46] unexpectedly had a higher continuation rate than the TCu 200. This is because higher copper content has been associated with more bleeding which contributes to early discontinuation.[50] The TCu 300 data were limited to two studies that both had total MMAT scores of 7,[44, 46] whereas the TCu 200 data had been obtained from seven studies with MMAT scores of 7,[36, 37, 40, 44] 6,[38] and 5[42] respectively.

Strengths and Limitations

This is the first systematic review to explore IUD types in younger aged nulliparous women. It has included all observational studies that provided information on IUD continuation or reasons for discontinuation in this user group. Non-restriction to RCTs may be considered a limitation, but a realist approach of expanding the inclusion criteria where RCT evidence is lacking could be commendable and more representative of routine practice. Using the MMAT, the quality of reviewed and included studies in this systematic review was good overall.

Articles for inclusion were unfortunately limited to publications in the English language. The absence of studies on IUDs currently available in the UK solely involving women aged under 30 warranted a deviation from the protocol to include all ages if women under 30 years were involved, and up to (≤) 30 years for the TCu 380A data and meta-analysis because of the ages of the Hall and Kutler study participants (18-30 years). Many studies did not report all the required information hence some included studies had missing information (Table 2). Most studies did not differentiate between nulligravid and nulliparous participants, many age ranges were not specific (e.g. ≤19 - ≥35), while some reports e.g. Sivin and Stern (1979) were of a combination of individual studies [45]. These have been appropriately stated and are not considered to impact the validity of the review.

Relevance of Findings

IUD use in young nulliparous women has been established to be safe, effective and acceptable.[51-53] It is recommended that women are provided the most appropriate IUD types for their uterine cavity size, with their uterine cavity width rather than length influencing IUD type choice.[28, 54-56] This systematic review emphasises this provision recommendation warrants further research and suggests IUD types for younger aged nulliparous women.

Recommendations

Strengthening evidence for contraceptive choice and continuation is needed to improve sexual health in younger aged women. Prospective observational studies that include various IUD designs and types, and detailed reporting of users' experiences could facilitate a better understanding of early IUD discontinuation and reasons for discontinuation based on IUD types. Studies designed to overcome the challenges of recruiting large numbers from varied demographic backgrounds, significant loss to follow up, and time or funding constraints are also likely to yield data widely applicable to IUC provision in and outside the UK.

CONCLUSION

Research is lacking on outcomes with the IUD types currently in use by young nulliparous women in the UK. Available evidence estimates a continuation rate of 81% at 12 months for the recommended standard-sized TCu 380A IUD in these women. More studies are needed to better estimate continuation rates for smaller-sized and flexible IUDs which may be higher in this user group. This in turn will help to improve sexual health in these women.

FIGURES

Figure 1 – PRISMA Flow Diagram

Figure 2 - TCu 380A continuation rates (excl Otero-Flores et al)

Figure 3 - TCu 380A continuation rates (incl Otero-Flores et al)

Figure 4 - Smaller TCu 380A continuation rates

Figure 5 - TCu 300 continuation rates

Figure 6 - TCu 200 continuation rates

Figure 7 – Nova T200 continuation rates

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The authors report no conflict of interest.

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See supplementary material 1.

DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

HA: research idea, study design, protocol, searches, first reviewer, data summary, writing - original draft, funding application for open access publishing, project administration; AJ: second reviewer, supervision, writing – review and editing, project administration; PB: searches, writing – review and editing; MM: meta-analysis, writing – original draft, review and editing; JR: contributed to research idea, study design, protocol, funding applications, and project administration, as well as supervision and writing – review and editing. All authors approved the final version.

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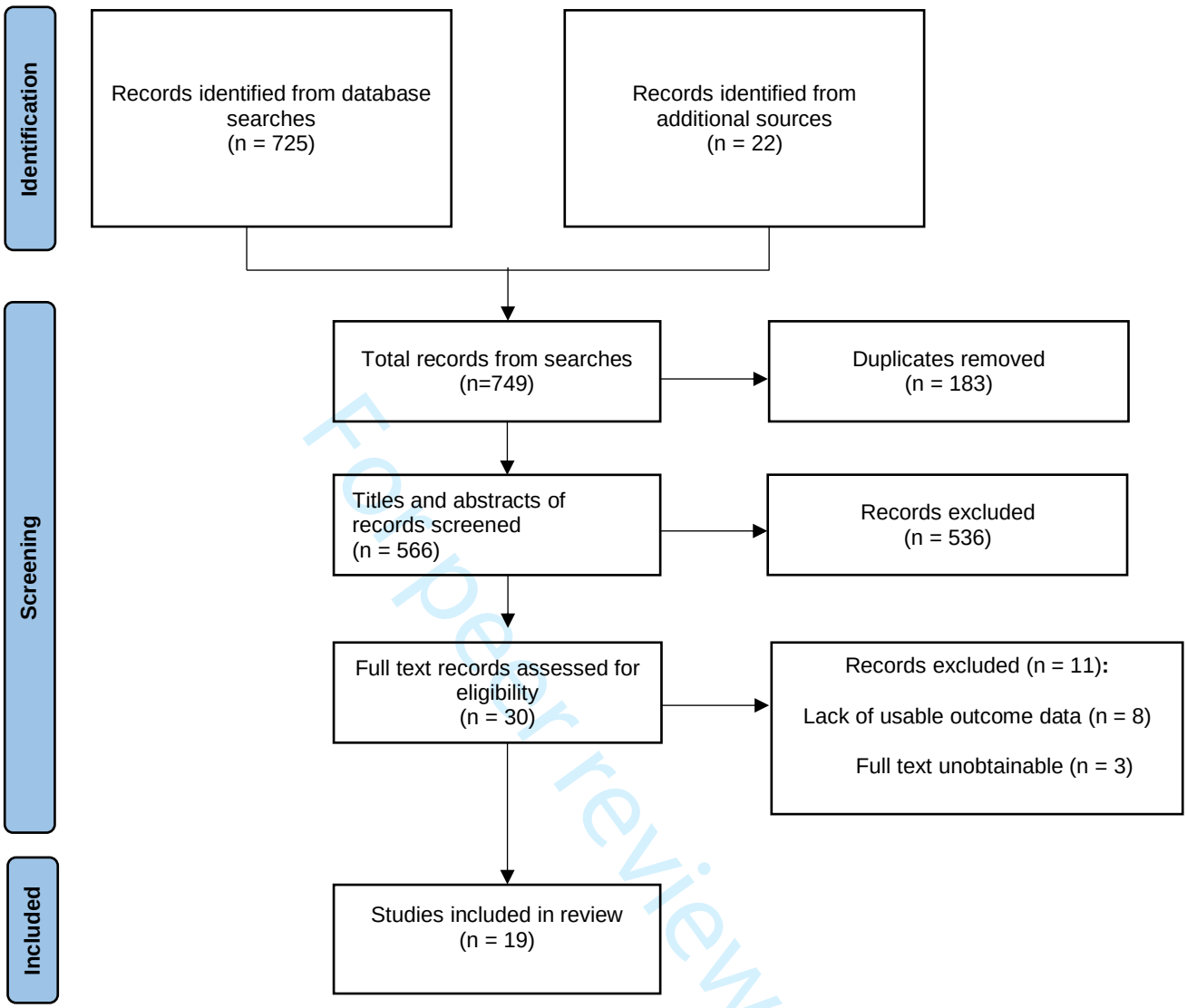
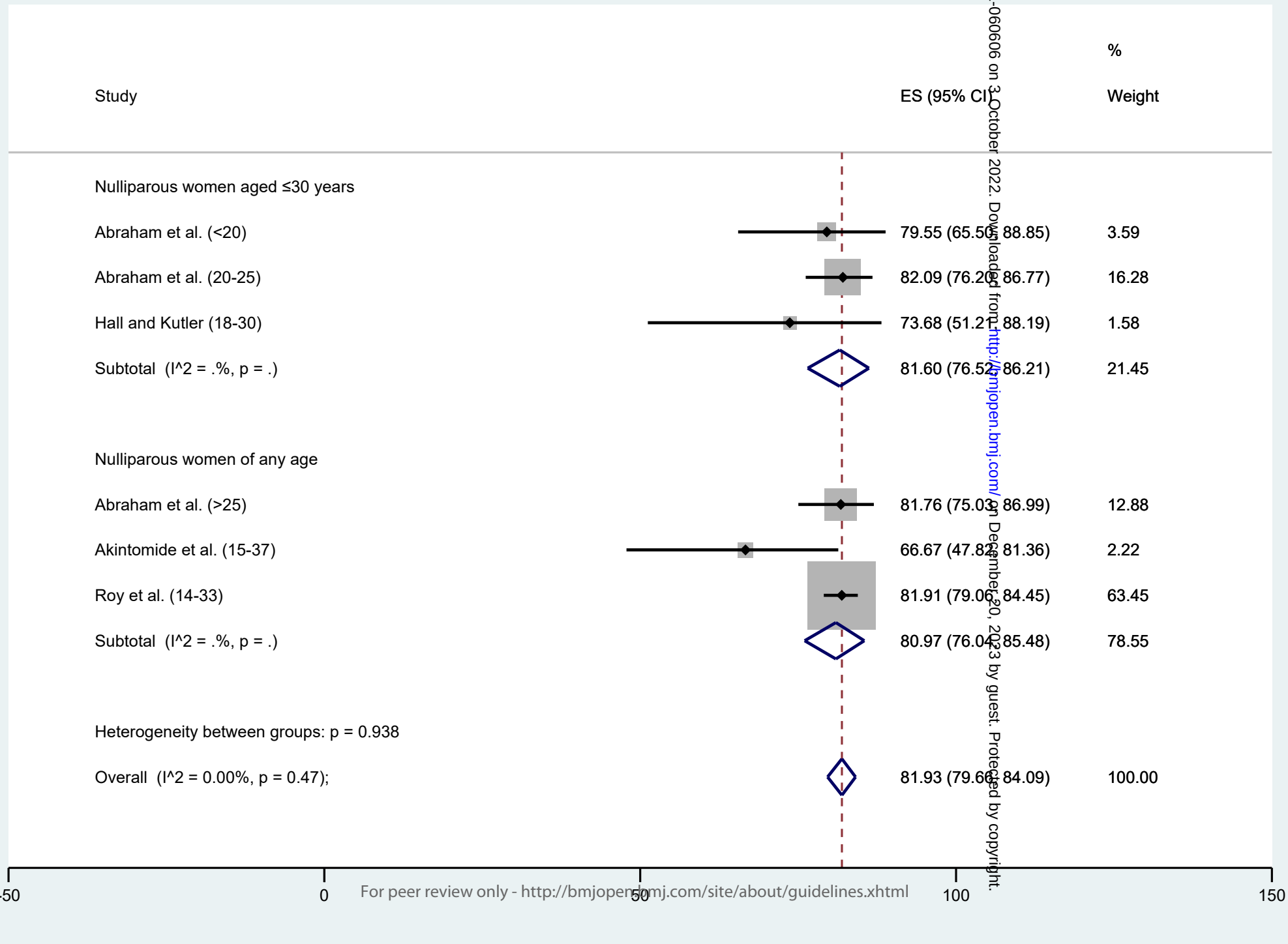
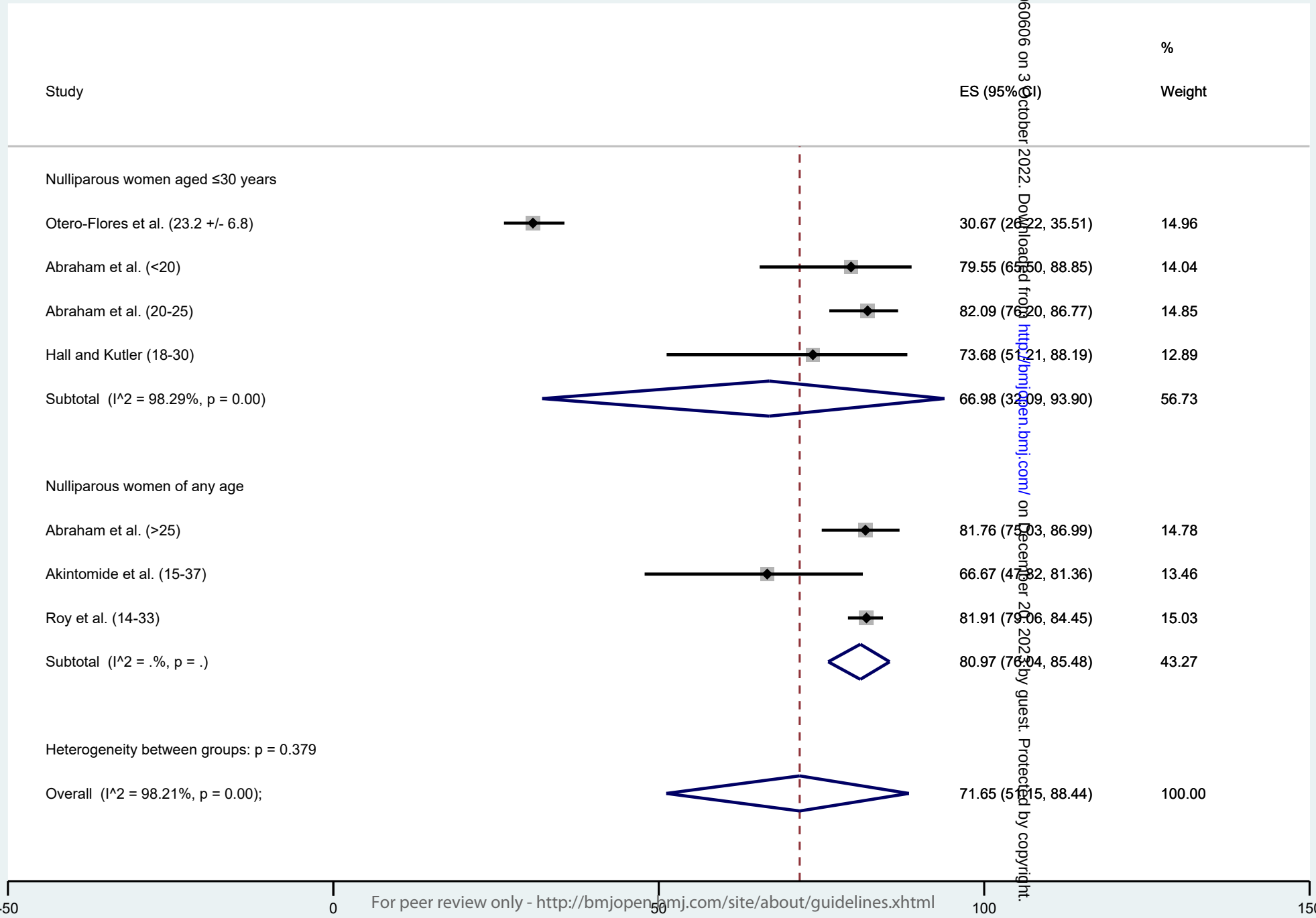


Figure 1 – PRISMA 2020 flow diagram of searches and selection of studies

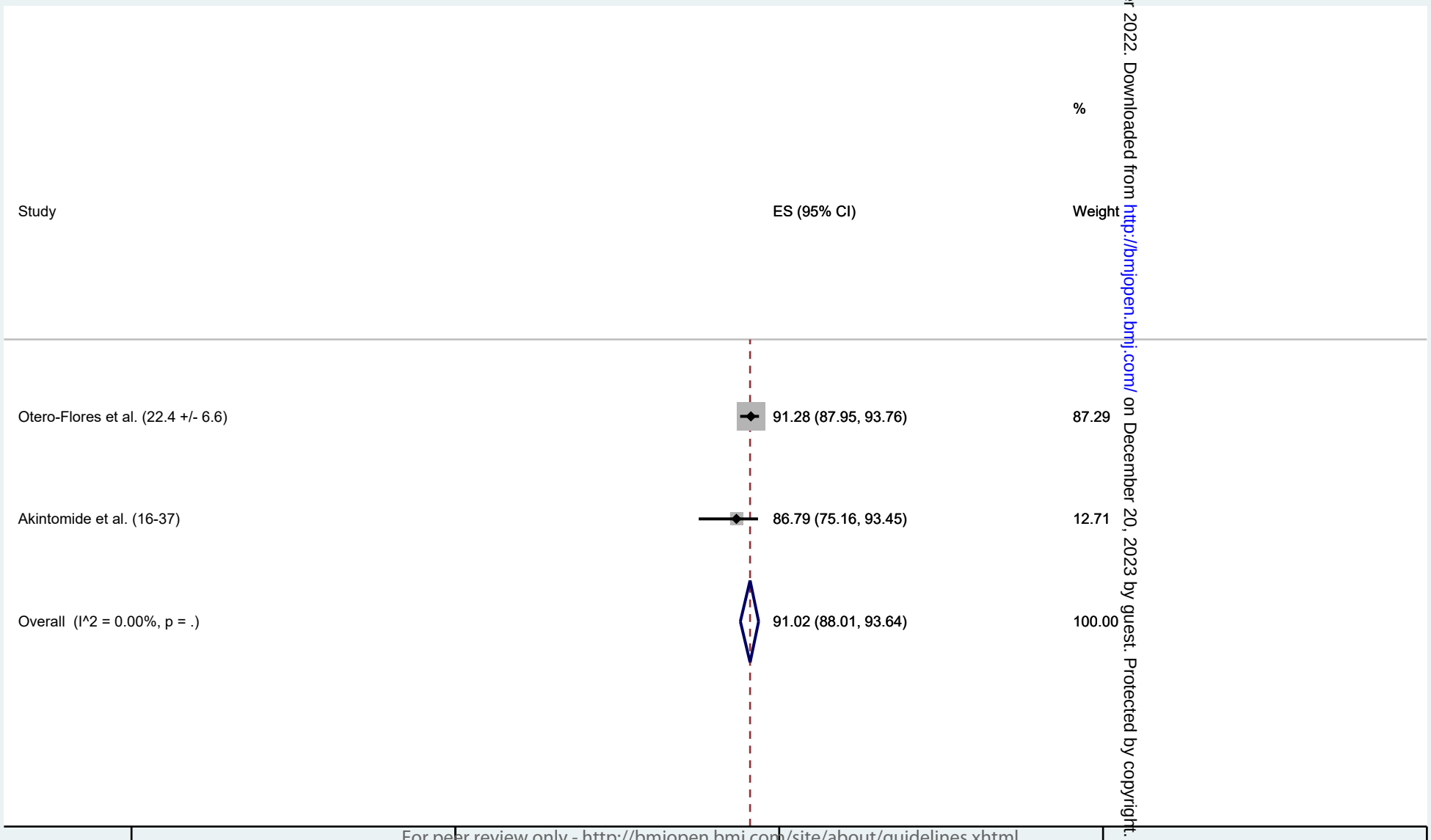
TCu 380A continuation rate at 12 months post-insertion (excl. Otero-Flores)



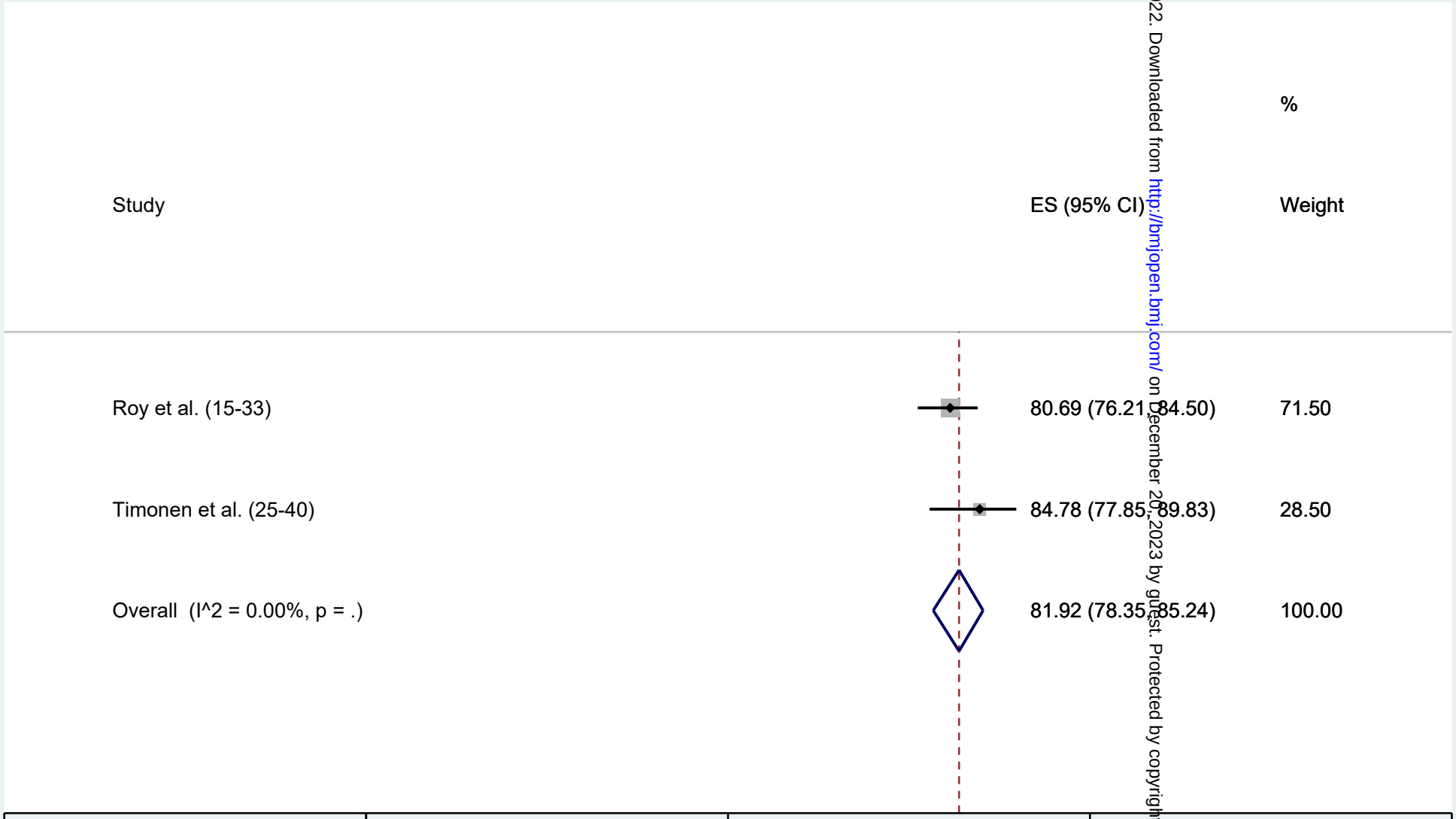
TCu 380A continuation rate at 12 months post-insertion (incl. Otero-Flores)



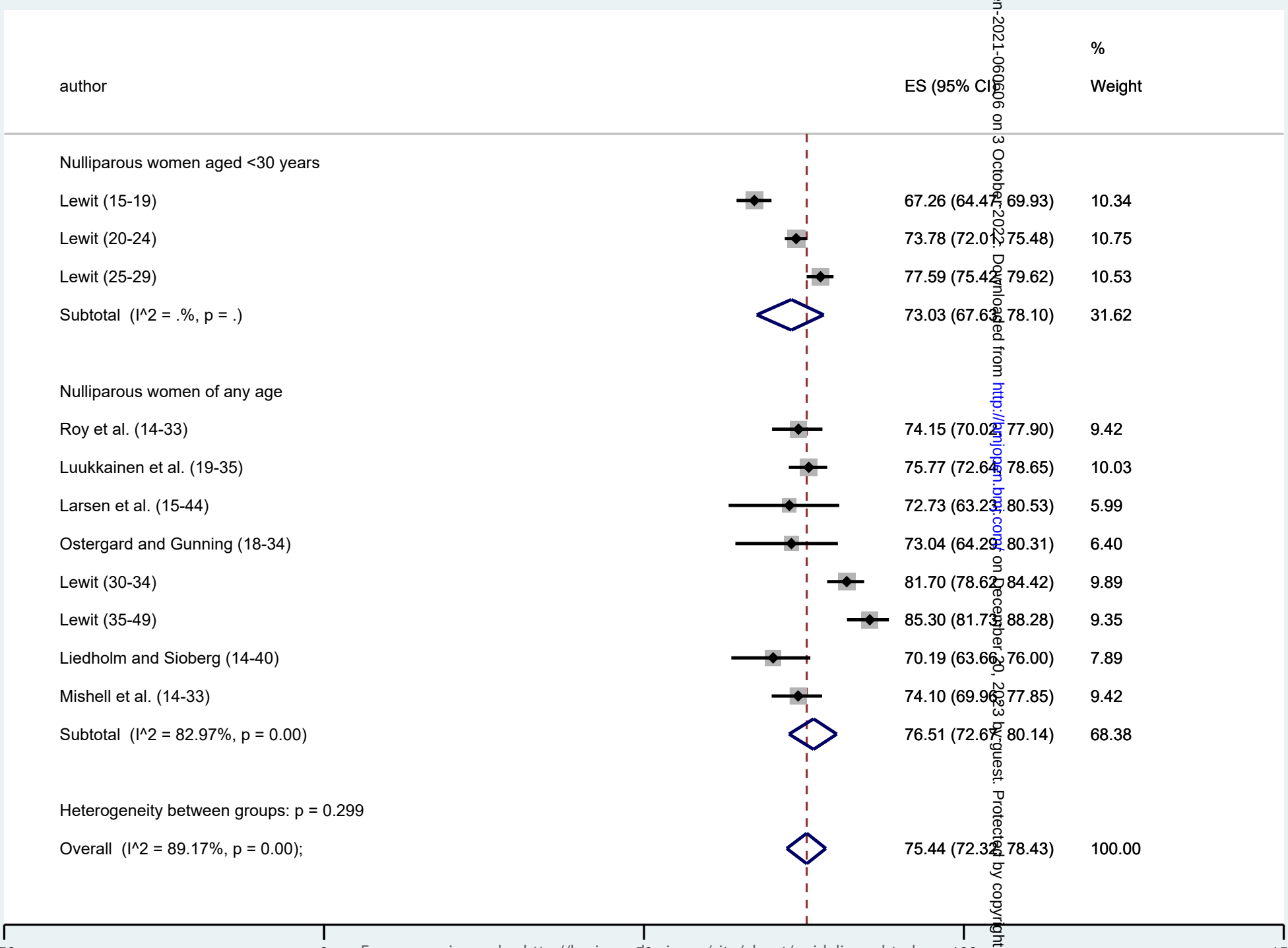
TCu 380A Nul/Mini TT380 slimline continuation rate at 12 months



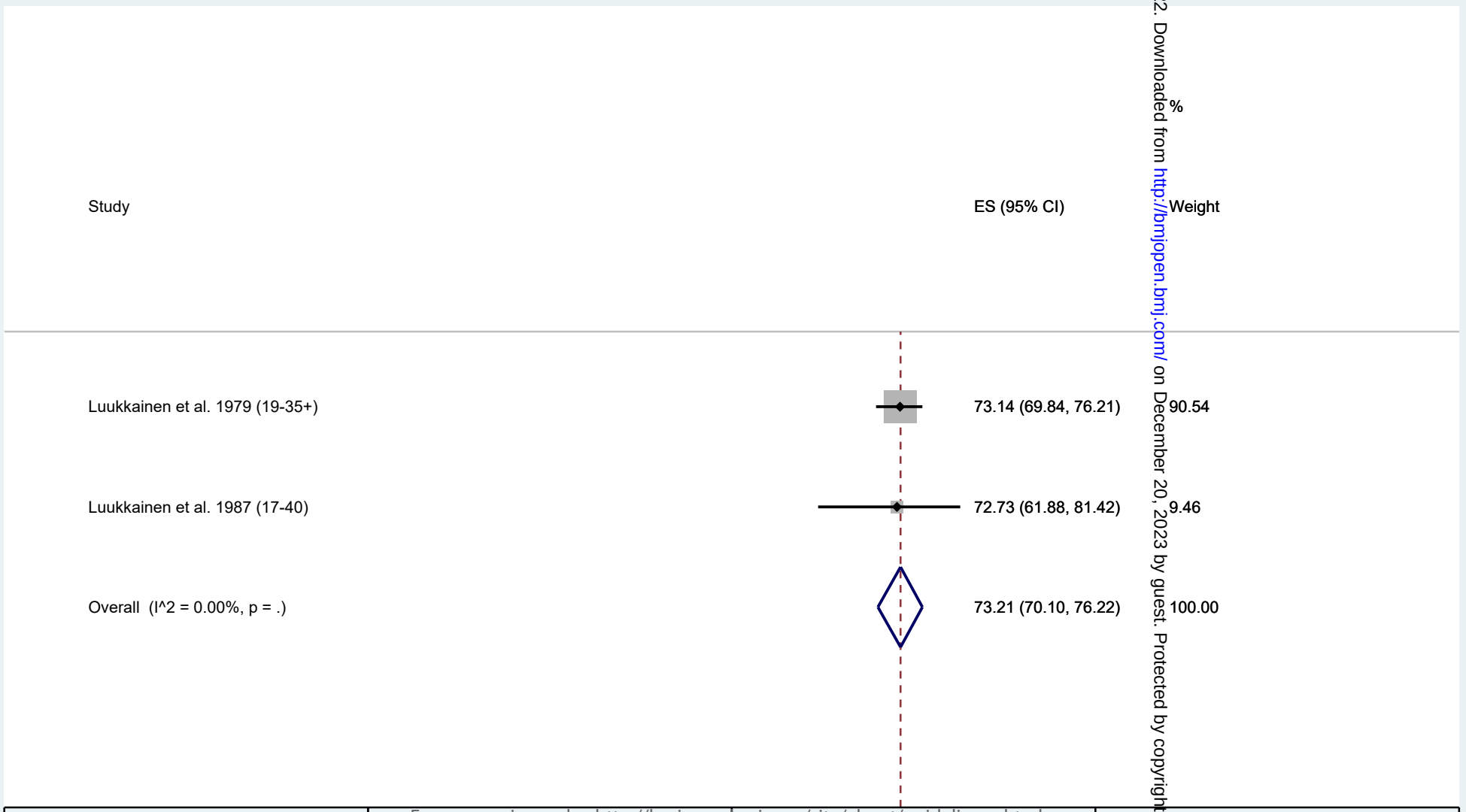
TCu 300 continuation rate at 12 months



TCu 200 continuation rate at 12 months



Nova T200 continuation rate at 12 months



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6 Supplementary material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 6-7 Supplementary material
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 6-7 Supplementary material
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6-7 Supplementary material
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7 Supplementary material
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7 Supplementary material
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 6-7 Supplementary material
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 6-7 Supplementary material
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7 Supplementary material

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 6-7 Supplementary material
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 6-7 Supplementary material
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 6-7 Supplementary material
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 6-7 Supplementary material
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 8-13 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 10 Supplementary material
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 13-9 Table 2-3 Figures 2 – 7 Supplementary material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 16-9 Figures 2 – 7 Supplementary material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 16-9 Figures 2–7 Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 16-9 Figures 2–7 Supplementary material
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 16-9 Figures 2–7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 19-20
	23b	Discuss any limitations of the evidence included in the review.	Page 19-20
	23c	Discuss any limitations of the review processes used.	Page 20
	23d	Discuss implications of the results for practice, policy, and future research.	Page 21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5 Supplementary material
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplementary material
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pages 5 and 8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 22
Competing interests	26	Declare any competing interests of review authors.	Page 22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Copper intrauterine contraception discontinuation in nulliparous and young women

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin

Citation

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin. Copper intrauterine contraception discontinuation in nulliparous and young women. PROSPERO 2019 CRD42019120969 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019120969

Review question

Which copper intrauterine devices are associated with higher discontinuation rates in young and nulliparous women?

Searches

Databases [including the Cochrane Library, the Database of Abstracts and Reviews of Effects (DARE), MEDLINE (Ovid), Excerpta Medica Database (EMBASE), Turning Research into Practice (TRIP) database and National Electronic Library of Health] and relevant websites [including Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, Medical Defence Unions, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar] will be searched using MeSH terms combined with key words for relevant articles published from 1966 to date. Reference lists of relevant articles will also be searched to identify more articles. The full texts of relevant articles will be screened, duplicates excluded and then data from selected articles included in the review.

Randomised controlled trials (RCTs) involving copper intrauterine devices (IUDs) available or comparable to those in the UK published in English will be included. Other studies that report on the main outcome (observational and qualitative studies) will be included and/or summarised if the number of RCTs eligible for inclusion are too few to answer the review question.

Key words

Copper intrauterine device related: copper intrauterine device, copper intrauterine contraceptive device, copper intrauterine contraception, copper coil, IUD

Nulliparous related: nulliparous, nulligravid, never pregnant, never delivered

Young women related: young women, adolescent, aged under, teenage

Types of study to be included

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved copper intrauterine devices available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over, or that involved copper intrauterine devices not available, or not of the same design and size to those available, in the UK.

Condition or domain being studied

Copper intrauterine contraception in nulliparous and young women

Participants/population

Women who are nulliparous and aged under 30

Intervention(s), exposure(s)

Copper intrauterine devices available or comparable to those in the UK

Comparator(s)/control

Any IUD, other contraceptive or no contraception where applicable

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Context

Copper intrauterine devices (IUDs) are of various shapes, sizes, copper surface area and copper distribution on the frame of the device. There are many types of IUDs available in the UK but none shown to be associated with better outcomes in nulliparous and young women. The identification and use of those IUDs associated with less discontinuation could improve outcomes including satisfaction and continuation rates of intrauterine contraception in nulliparous and younger women.

Main outcome(s)

Copper intrauterine contraception discontinuation rates in nulliparous and young women based on type of IUD

Timing and effect measures

Additional outcome(s)

Reasons for IUD discontinuation

Timing and effect measures

Data extraction (selection and coding)

The abstracts of published articles obtained from the literature and websites searches will be reviewed by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. All retrieved full texts of published articles will be reviewed to agree which studies to include in the systematic review, with disagreements resolved by the third author. All retrieved articles to be included in the systematic review will undergo a quality assessment using a risk of bias tool applicable to the type of study.

Main data to be extracted:

type of copper intrauterine device (IUD)

age of women

gravidity/parity of women

place/time of IUD insertion

IUD discontinuation rate(s)

reason(s) for IUD discontinuation

Risk of bias (quality) assessment

All retrieved articles to be included in the systematic review will undergo a quality assessment. One author will complete the inclusion criteria checklist while the second author will review the checklist, with disagreements resolved by the third author/consensus. Retrieved articles with a high risk of bias will be excluded from the systematic review.

Strategy for data synthesis

Data from the included studies will be extracted using a standardised form by one author while the second author will check these. Disagreements will be resolved by a further review of the study with the third author and consensus. One author will enter the extracted data into Review Manager (RevMan®) Software while the second author will again check these for accuracy. It is planned that aggregate data will be used. However, individual data on the intervention and population of interest (IUDs in nulliparous and young women aged under 30) will be extracted where studies have reported on this subgroup their outcomes in conjunction with other population subgroups or study outcomes.
A quantitative synthesis is planned based on the expected homogeneity of the data to be obtained for the main outcome to be studied. This homogeneous data will be combined for meta-analysis. Heterogeneous

data, some of which is expected to be obtained on the additional outcome, will be narratively synthesised.

Analysis of subgroups or subsets
IUDs of same size and design will be grouped and discontinuation rates presented based on IUD type.

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Anticipated or actual start date
28 January 2019

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31 January 2020

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Nil

Conflicts of interest

Language
English

Country
England

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Contraception; Copper; Female; Humans; Intrauterine Devices; Parity; Pregnancy

Date of registration in PROSPERO
07 February 2019

Date of publication of this version
07 February 2019

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

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Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

07 February 2019

Table – Search Strategies

Databases and additional sources search	Search term(s) used	Limits	Records identified
Allied and Complementary Medicine (AMED) British Nursing Index (BNI) Cumulative Index to Nursing and Allied Health Literature (CINAHL) Excerpta Medica Database (EMBASE) Nursing and Allied Health Professionals Database (EMCARE) Health Management Information Consortium (HMIC) General Medical Database (MEDLINE) Psychology and Allied Fields (PsychINFO) PubMed	(copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab	Title, Abstract English language	**725**
The Cochrane Library Database of Abstracts and Reviews of Effects (DARE) Turning Research into Practice (TRIP) Bandolier National Electronic Library of Health Medicines and Healthcare products Regulatory Agency (MHRA) Faculty of Sexual and Reproductive Healthcare (FSRH) Royal College of Obstetricians and Gynaecologists (RCOG) Department of Health National Institute for Health and Care Excellence (NICE) Scottish Intercollegiate Guidelines, World Health Organisation (WHO)	'copper intrauterine'	-	**22**
Google Scholar	'copper intrauterine device young nulliparous'	-	

TCu 380A continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(81.60% (95% CI 76.52-86.21%))**
Excluding Abraham et al. (<20)	82.04% (95% CI 76.48-87.04%)
Excluding Abraham et al. (20-25)	78.01% (95% CI 66.60-87.74%)
Excluding Hall and Kutler (18-30)	81.83% (95% CI 76.66-86.49%)
Subgroup 2 (Nulliparous women of any age)	**(80.97% (95% CI 76.04-85.48%))**
Excluding Abraham et al. (>25)	81.99% (95% CI 79.19-84.63%)
Excluding Akintomide et al. (15-37)	81.94% (95% CI 79.41-84.34%)
Excluding Roy et al. (14-33)	80.12% (95% CI 73.92-85.70%)
Overall effect size (all studies)	**(81.93% (95% CI 79.66-84.09%))**
Excluding Abraham et al. (<20)	81.84% (95% CI 79.13-84.40%)
Excluding Abraham et al. (20-25)	81.44% (95% CI 78.16-84.53%)
Excluding Hall and Kutler (18-30)	81.87% (95% CI 79.60-84.03%)
Excluding Abraham et al. (>25)	81.57% (95% CI 78.38-84.58%)
Excluding Akintomide et al. (15-37)	82.14% (95% CI 79.87-84.31%)
Excluding Roy et al. (14-33)	80.92% (95% CI 76.93-84.64%)

TCu 200 continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(73.03% (95% CI 67.63-78.10%))**
Excluding Lewit (15-19)	75.26% (95% CI 73.90-76.59%)
Excluding Lewit (20-24)	73.33% (95% CI 71.62-75.00%)
Excluding Lewit (25-29)	71.78% (95% CI 70.30-73.24%)
Subgroup 2 (Nulliparous women of any age)	**(76.51% (95% CI 72.67-80.14%))**
Excluding Roy et al. (14-33)	76.83% (95% CI 72.49-80.91%)
Excluding Luukkainen et al. (19-35)	76.53% (95% CI 71.86-80.91%)
Excluding Larsen et al. (15-44)	76.85% (95% CI 72.79-80.67%)
Excluding Ostergard and Gunning (18-34)	76.84% (95% CI 72.76-80.69%)
Excluding Lewit (30-34)	75.59% (95% CI 71.42-79.54%)
Excluding Lewit (35-49)	75.20% (95% CI 71.98-78.29%)
Excluding Liedholm and Sioberg (14-40)	77.32% (95% CI 73.40-81.01%)
Excluding Mishell et al. (14-33)	76.84% (95% CI 72.51-80.91%)
Overall effect size (all studies)	**(75.44% (95% CI 72.32-78.43%))**
Excluding Lewit (15-19)	76.43% (95% CI 73.71-79.04%)
Excluding Lewit (20-24)	75.59% (95% CI 71.81-79.17%)
Excluding Lewit (25-29)	76.16% (95% CI 71-60-78.56%)
Excluding Roy et al. (14-33)	75.56% (95% CI 72.16-78.81%)
Excluding Luukkainen et al. (19-35)	75.38% (95% CI 71.89-78.72%)
Excluding Larsen et al. (15-44)	75.60% (95% CI 72.34-78.70%)
Excluding Ostergard and Gunning (18-34)	75.59% (95% CI 72.33-78.71%)
Excluding Lewit (30-34)	74.72% (95% CI 71.59-77.73%)

Excluding Lewit (35-49)	74.37% (95% CI 71.53-77.10%)
Excluding Liedholm and Sioberg (14-40)	75.87% (95% CI 72.61-78.98%)
Excluding Mishell et al. (14-33)	75.56% (95% CI 72.16-78.81%)

TCu 200 discontinuation at 12 months due to pain/bleeding – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(7.05% (95% CI 5.59-8.65%))**
Excluding Lewit (15-19)	7.31% (95% CI 6.52-8.14%)
Excluding Lewit (20-24)	6.31% (95% CI 5.41-7.27%)
Excluding Lewit (25-29)	7.88% (95% CI 7.02-8.78%)
Subgroup 2 (Nulliparous women of any age)	**(12.77% (95% CI 8.48-17.78%))**
Excluding Roy et al. (14-33)	13.10% (95% CI 8.10-19.06%)
Excluding Luukkainen et al. (19-35)	11.02% (95% CI 8.41-13.92%)
Excluding Larsen et al. (15-44)	12.40% (95% CI 7.87-17.76%)
Excluding Ostergard and Gunning (18-34)	12.86% (95% CI 8.20-18.35%)
Excluding Lewit (30-34)	13.61% (95% CI 8.83-19.22%)
Excluding Lewit (35-49)	13.79% (95% CI 9.10-19.25%)
Excluding Liedholm and Sioberg (14-40)	12.08% (95% CI 7.56-17.45%)
Excluding Mishell et al. (14-33)	13.13% (95% CI 8.13-19.08%)
Overall effect size (all studies)	**(10.87% (95% CI 7.98-14.15%))**
Excluding Lewit (15-19)	11.37% (95% CI 8.08-15.12%)
Excluding Lewit (20-24)	11.23% (95% CI 7.70-15.32%)
Excluding Lewit (25-29)	11.52% (95% CI 8.34-15.14%)
Excluding Roy et al. (14-33)	10.90% (95% CI 7.77-14.47%)
Excluding Luukkainen et al. (19-35)	9.32% (95% CI 7.62-11.17%)
Excluding Larsen et al. (15-44)	10.51% (95% CI 7.58-13.86%)
Excluding Ostergard and Gunning (18-34)	10.78% (95% CI 7.77-14.20%)
Excluding Lewit (30-34)	11.23% (95% CI 8.01-14.92%)
Excluding Lewit (35-49)	11.34% (95% CI 8.17-14.94%)
Excluding Liedholm and Sioberg (14-40)	10.26% (95% CI 7.40-13.53%)
Excluding Mishell et al. (14-33)	10.92% (95% CI 7.78-14.50%)

TCu 200 discontinuation at 12 months due to expulsion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(10.52% (95% CI 7.17-14.41%))**
Excluding Lewit (15-19)	8.59% (95% CI 7.74-9.48%)
Excluding Lewit (20-24)	11.21% (95% CI 10.03-12.44%)
Excluding Lewit (25-29)	10.36% (95% CI 9.38-11.38%)
Subgroup 2 (Nulliparous women of any age)	**(4.93% (95% CI 2.93-7.39%))**
Excluding Roy et al. (14-33)	4.85% (95% CI 2.57-7.78%)
Excluding Luukkainen et al. (19-35)	4.17% (95% CI 2.68-5.96%)
Excluding Larsen et al. (15-44)	4.92% (95% CI 2.79-7.58%)
Excluding Ostergard and Gunning (18-34)	4.80% (95% CI 2.69-7.46%)
Excluding Lewit (30-34)	4.74% (95% CI 2.41-7.76%)
Excluding Lewit (35-49)	5.24% (95% CI 3.03-7.99%)
Excluding Liedholm and Sioberg (14-40)	5.84% (95% CI 3.95-8.07%)

Excluding Mishell et al. (14-33)	4.85% (95% CI 2.57-7.77%)
Overall effect size (all studies)	**(6.44% (95% CI 4.49-8.69%))**
Excluding Lewit (15-19)	5.76% (95% CI 4.14-7.61%)
Excluding Lewit (20-24)	6.16% (95% CI 3.87-8.93%)
Excluding Lewit (25-29)	6.16% (95% CI 3.96-8.79%)
Excluding Roy et al. (14-33)	6.55% (95% CI 4.47-8.99%)
Excluding Luukkainen et al. (19-35)	6.01% (95% CI 3.98-8.42%)
Excluding Larsen et al. (15-44)	6.54% (95% CI 4.51-8.91%)
Excluding Ostergard and Gunning (18-34)	6.46% (95% CI 4.43-8.83%)
Excluding Lewit (30-34)	6.47% (95% CI 4.36-8.95%)
Excluding Lewit (35-49)	6.87% (95% CI 4.87-9.18%)
Excluding Liedholm and Sioberg (14-40)	7.29% (95% CI 5.39-9.45%)
Excluding Mishell et al. (14-33)	6.55% (95% CI 4.47-8.99%)

TCu 200 discontinuation at 12 months due to pregnancy – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(2.19% (95% CI 1.47-3.05%))**
Excluding Lewit (15-19)	2.27% (95% CI 1.82-2.75%)
Excluding Lewit (20-24)	1.83% (95% CI 1.35-2.39%)
Excluding Lewit (25-29)	2.63% (95% CI 2.13-3.18%)
Subgroup 2 (Nulliparous women of any age)	**(1.15% (95% CI 0.54-1.95%))**
Excluding Roy et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Excluding Luukkainen et al. (19-35)	0.96% (95% CI 0.38-1.75%)
Excluding Larsen et al. (15-44)	1.18% (95% CI 0.53-2.05%)
Excluding Ostergard and Gunning (18-34)	1.31% (95% CI 0.65-2.16%)
Excluding Lewit (30-34)	1.35% (95% CI 0.70-2.18%)
Excluding Lewit (35-49)	1.31% (95% CI 0.62-2.20%)
Excluding Liedholm and Sioberg (14-40)	1.00% (95% CI 0.42-1.78%)
Excluding Mishell et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Overall effect size (all studies)	**(1.49% (95% CI 0.96-2.13%))**
Excluding Lewit (15-19)	1.39% (95% CI 0.81-2.09%)
Excluding Lewit (20-24)	1.34% (95% CI 0.83-1.94%)
Excluding Lewit (25-29)	1.48% (95% CI 0.87-2.22%)
Excluding Roy et al. (14-33)	1.46% (95% CI 0.89-2.16%)
Excluding Luukkainen et al. (19-35)	1.40% (95% CI 0.83-2.09%)
Excluding Larsen et al. (15-44)	1.53% (95% CI 0.98-2.19%)
Excluding Ostergard and Gunning (18-34)	1.62% (95% CI 1.07-2.26%)
Excluding Lewit (30-34)	1.69% (95% CI 1.18-2.29%)
Excluding Lewit (35-49)	1.64% (95% CI 1.10-2.28%)
Excluding Liedholm and Sioberg (14-40)	1.41% (95% CI 0.88-2.06%)
Excluding Mishell et al. (14-33)	1.46% (95% CI 0.89-2.16%)

Table – Characteristics of studies excluded following full text assessment

Study / Authors	Year	Country	Study Design	Study Objectives	Reasons for Exclusion
Akintomide et al[5]	2021	Austria, Finland, Germany, Poland, Sweden, UK	Prospective cohort	Secondary analysis of continuation, unwanted effects and cost consequences at 1 year in IUD users ≤30 in the European Active Surveillance Study for Intrauterine Devices	Undifferentiable results - IUD type categories based on IUD characteristics rather than brand or name of IUD
Garbers et al[19]	2013	USA	Retrospective records review	Prevalence and predictors of IUD discontinuation at 6 months in 306 Cu T380A users	Undifferentiable results; varied duration; 23 excluded from continuation analysis
Goldstuck[20]	1980	UK	Prospective cohort (selected)	Clinical evaluation of the combined multiload copper 250-mini IUD in selected nulliparous women	Undifferentiable results; disparity between data in tables and text
Hindle[26]	1978	Unable to confirm		Clinical evaluation and follow-up on 3,829 IUD procedures	Full text unobtainable
Lete et al[21]	1998	Spain	Prospective cross-sectional	Evaluation of IUD use in nulliparous women compared to parous women over a 12-year period	Data reported as incidence of events rather than rates
Ogedengbe et al[22]	1991	Nigeria	Prospective cohort	A comparison efficacy and discontinuation at 1 year of multiload and copper-T IUDs sequentially assigned to users	Parity of participants not detailed (mean parity 4); only one nulliparous participant
Patnaik[27]	2003	India	Unable to confirm	Uptake, satisfaction, retention and reasons for discontinuation of the copper T IUD	Full text unobtainable
Petersen et al[28]	1991	Unable to confirm	RCT – double blind	Significance of endometrial cavity length in the clinical performance of IUDs in nulligravidae	Full text unobtainable
Phillips et al[23]	2017	USA	Retrospective records review	Comparison of continuation and performance of levonorgestrel and copper intrauterine devices over 5 years	Undifferentiable results
Sivin and Tatum[24]	1981	USA	Prospective cohort	Clinical performance of the TCu 380A IUD over 4 years	Undifferentiable results
Teal et al[25]	2015	USA	Retrospective records review	Evaluation of the success and safety of intrauterine device (IUD) placement in adolescents based on age and parity	Undifferentiable results

References

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19. Garbers S, Haines-Stephan J, Lipton Y, et al, Continuation of copper-containing intrauterine devices at 6 months. Contraception, 2013. 87(1): p. 101-106.

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Table – Quality Assessment of Included Studies Using the Mixed Methods Appraisal Tool (MMAT) version 2018

Study / Authors	*Design Category*	*Responses to MMAT Questions (and Scores: Yes (1) / No (0) / Can't Tell (0)*							
		Screening 1	**Screening 2**	**Appraisal 1**	**Appraisal 2**	**Appraisal 3**	**Appraisal 4**	**Appraisal 5**	**Total**
Abraham et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Akintomide et al 2019	Quantitative, non-randomised	yes	yes	yes	yes	no	yes	yes	6
Allonen et al 1980	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Elkhateeb et al 2020	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Fugere 1990	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Hall and Kutler 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Kaislasuo et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Larsen et al 1981	Quantitative, randomised	yes	yes	can't tell	yes	yes	no	yes	5
Lewit 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Liedholm and Sjoberg 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Luukkainen et al 1979	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Luukkainen et al 1987	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Mishell et al 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Nygren et al 1981	Quantitative, randomised	yes	yes	yes	yes	yes	yes	yes	7
Ostergard and Gunning 1979	Quantitative, randomised	yes	yes	yes	can't tell	yes	no	yes	5
Otero-Flores et al 2003	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Roy et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Sivin and Stern 1979	Quantitative, randomised	yes	yes	can't tell	can't tell	yes	yes	yes	5
Timonen et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7

Supplementary material – Doi plots

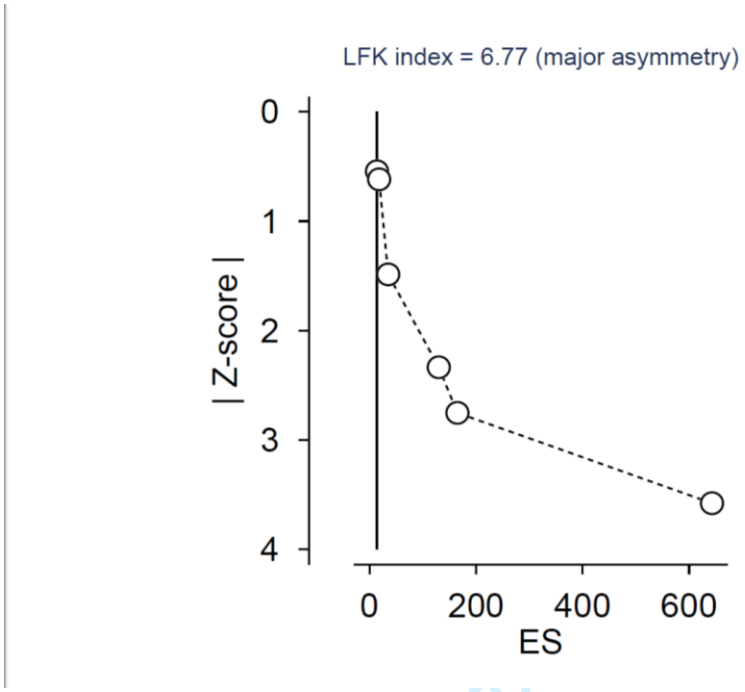

Figure 1 - Doi plot for TCu 380A continuation at 12 months

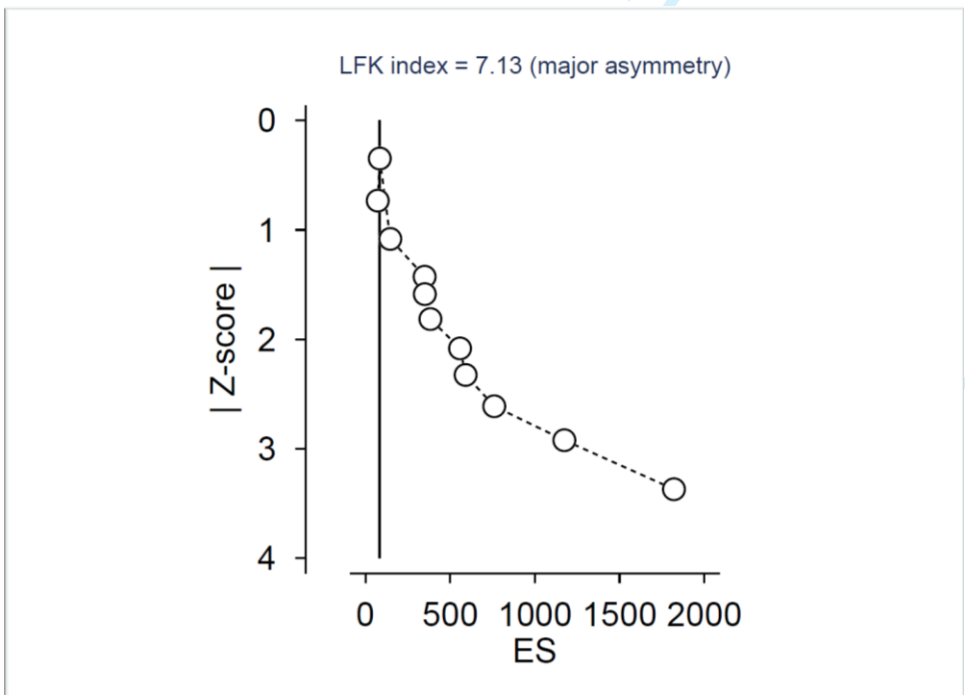

Figure 2 – Doi plot for TCu 200 continuation at 12 months

Supplementary material – Doi plots

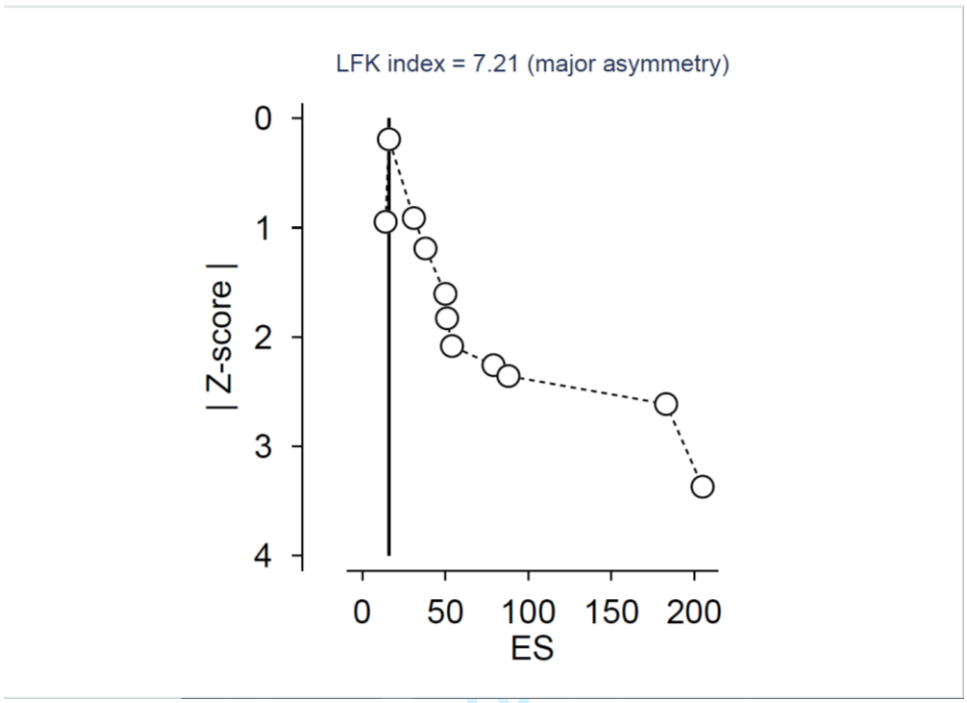

Figure 3 – Doi plot for TCu 200 discontinuation at 12 months due to bleeding/pain

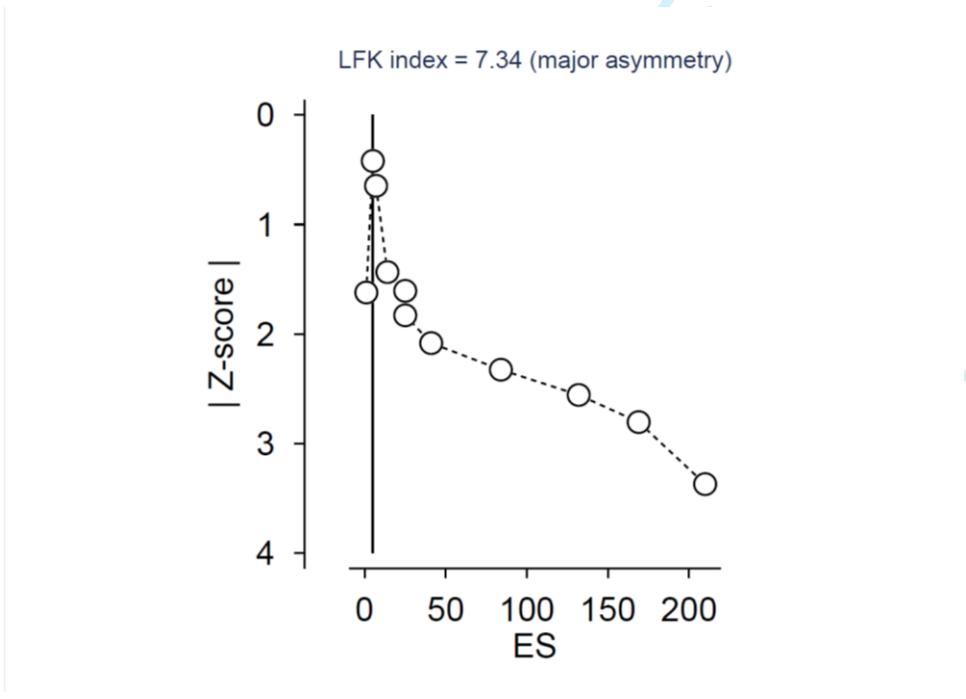

Figure 4 – Doi plot for TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – Doi plots

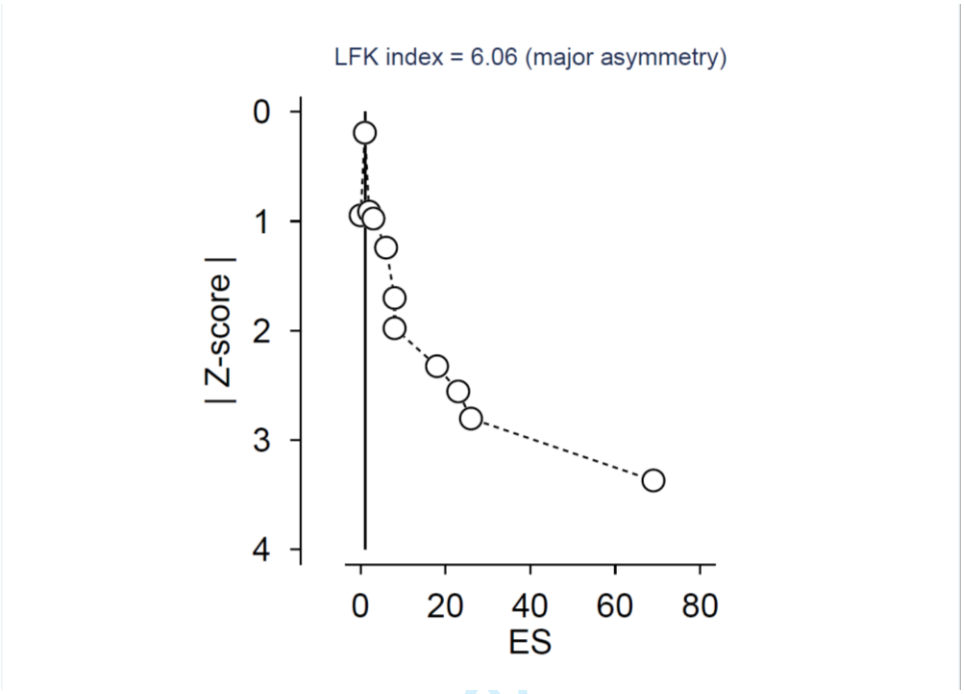

Figure 5 – Doi plot for TCu 200 discontinuation due to pregnancy

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

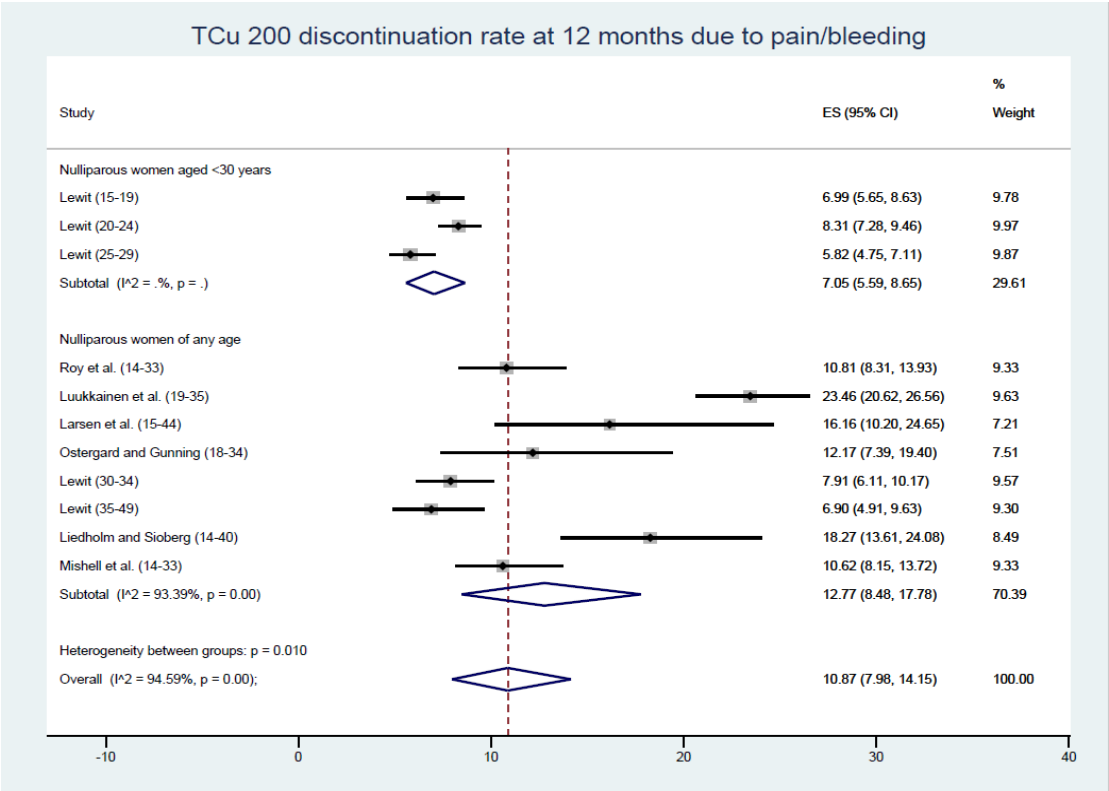

Figure 1 - TCu 200 discontinuation at 12 months due to pain/bleeding

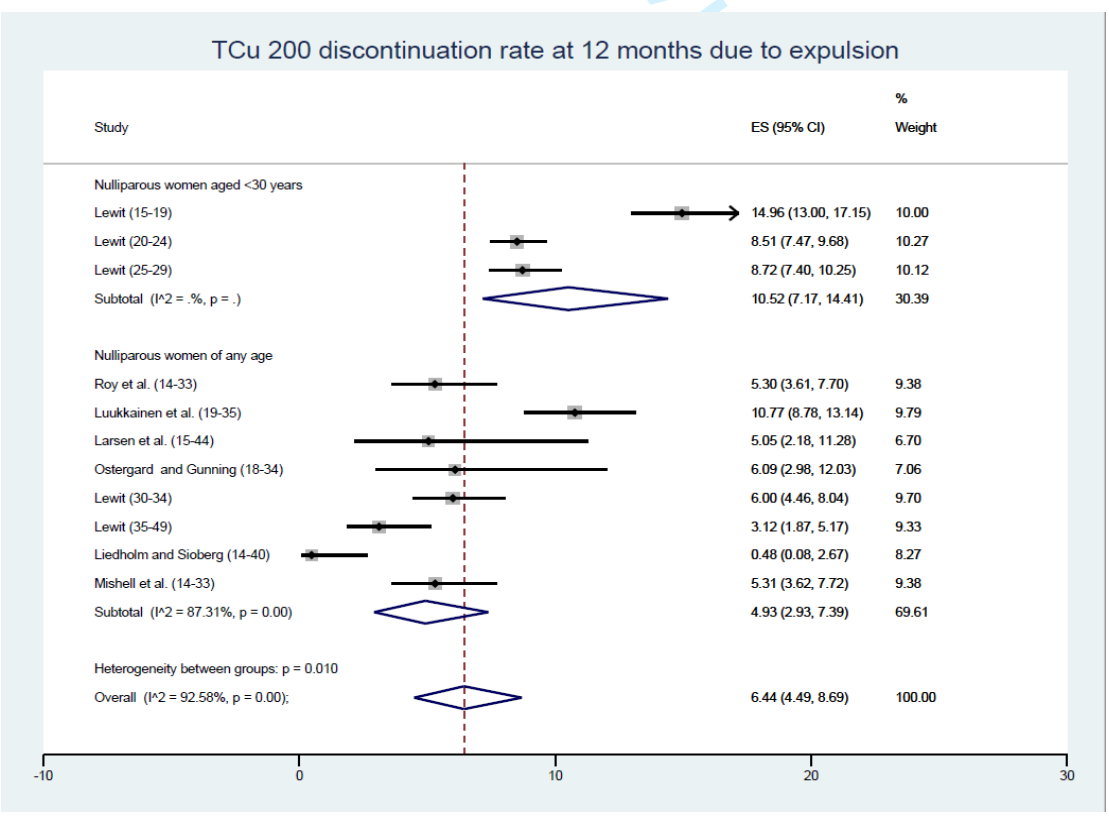

Figure 2 – TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

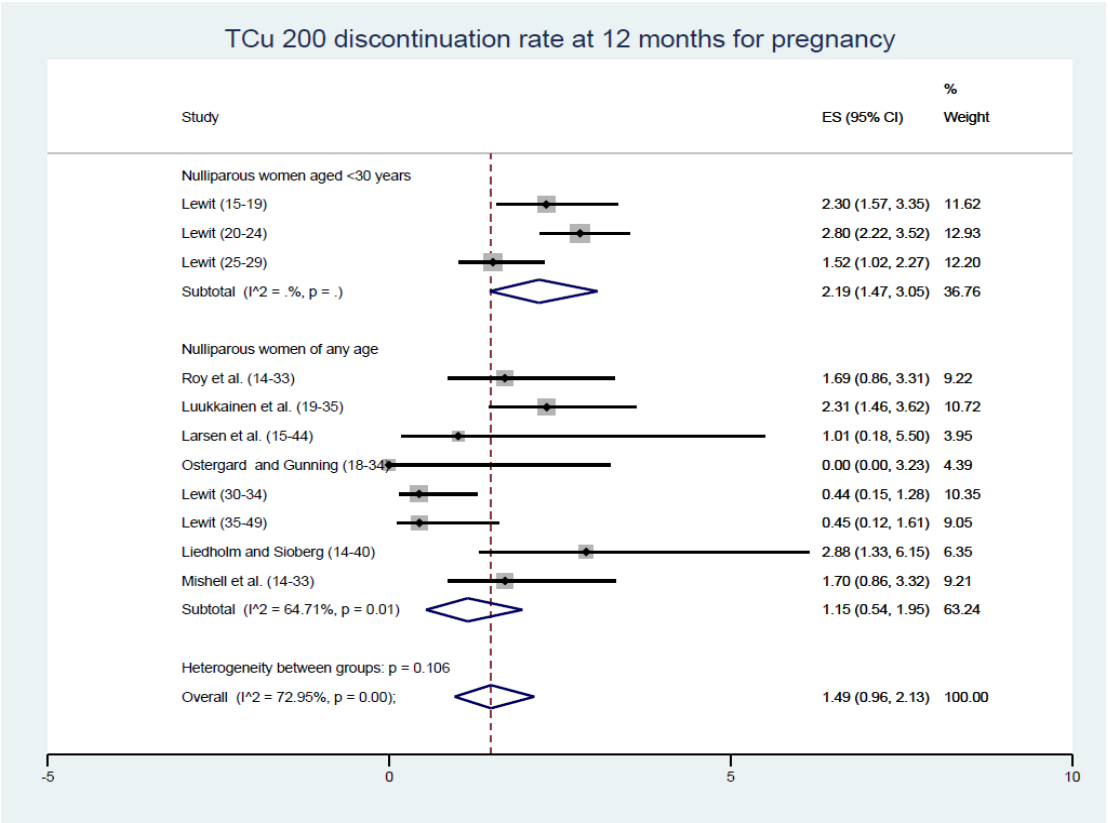

Figure 3 – TCu 200 discontinuation at 12 months due to pregnancy

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A systematic review of copper intrauterine contraception continuation in young nulliparous women based on intrauterine device type

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TITLE PAGE

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on intrauterine device type

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Short Title: Review of IUD continuation rates in young nulliparous women

ABSTRACT

Objectives

No copper intrauterine device (IUD) type is known to better suit young nulliparous women who tend to experience higher rates of IUD discontinuation compared to their older parous counterparts. A systematic review to determine which IUDs have higher continuation rates in young nulliparous women was undertaken.

Design

Systematic review and meta-analyses of available evidence based on IUD type.

Data sources

AMED, BNI, CINAHL, DARE, EMBASE, EMCARE, HMIC, MEDLINE, PsychINFO, PubMed, TRIP, the Cochrane Library electronic databases were searched from inception to 11 May 2022; as well as the Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar websites.

Eligibility criteria

All studies on IUDs currently available in the UK or comparable (same design and size) to those available in the UK involving nulliparous women of any age including those aged under 30.

Data extraction and synthesis

Independently extracted data were assessed as low risk of bias using the Mixed Methods Appraisal Tool. Random effects meta-analyses of proportions were performed where data including subgroups were amenable to quantitative synthesis. Heterogeneity was reported using tau^2 and I^2 statistics, and sensitivity analyses were also performed.

Results

Nineteen studies involving 13,045 nulliparous women were included but the heterogeneity of participant ages, parity and IUD types made quantitative synthesis of outcome data in totality inappropriate. The highest continuation rate obtained was 91.02% [95% CI 88.01-93.64%] for the smaller TCu 380A at 12 months post insertion.

Conclusions

Evidence for IUD use in young nulliparous women based on IUD type remains limited. Smaller-sized IUD types appear better suited to this group of IUD users however more research is needed.

PROSPERO registration number CRD42019120969.

SHORT TITLE: Review of IUD continuation rates in young nulliparous women

KEY WORDS: IUD, continuation, discontinuation, reasons, young, nulliparous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first reported systematic review exploring IUD types in young nulliparous women
- A wide range of data sources unrestricted to randomised controlled trials was reviewed – an approach more representative of the real world
- Articles for inclusion were limited to publications in the English language
- Some data were obtained by calculation and measurements of graphs or figures where this was not numerically specified in reports
- Most studies did not differentiate between nulligravid and nulliparous participants

REPORTING STATEMENT CHECKLIST

See supplementary material 1

MAIN TEXT: (4234 words)

INTRODUCTION

The highest rates of unintended pregnancy and terminations of pregnancy, which contribute to poor sexual health, are in women aged 20-24 followed by those aged 25-29.[1] Increasing uptake of long-acting reversible contraceptives (LARC) like copper intrauterine contraception in these women is yet to yield a proportional reduction in pregnancy terminations, attributable to their higher LARC discontinuation rates.[2]

Copper intrauterine contraception is the LARC with the greatest number of brands, with 21 copper intrauterine devices (IUDs) available in the UK.[3] IUDs are of various shapes, sizes, total copper surface area and copper distribution on the IUD frame. They have changed little over the last 40 years. No IUD type has been shown to be associated with better outcomes regarding continuation or unwanted effects that lead to early IUD discontinuation. This early IUD discontinuation excludes discontinuation due to IUD user choice alone or the wish to conceive. IUD continuation rates tend to be surrogate for IUD satisfaction and/or acceptability. Studies have shown IUD continuation to be lower with unfavourable outcomes related to unwanted effects in adolescents and women in their 20s compared to their older counterparts, as well as in nulliparous compared to parous women.[4-8]

Previous systematic reviews and guidance suggest that IUD size and shape may be a factor in discontinuation and have recommended future research investigate which IUD types are associated with less pain, bleeding and discontinuation.[7, 9-11] The identification and use of those IUDs with higher continuation and fewer unwanted effects could improve outcomes including IUD satisfaction and continuation rates in young nulliparous women.

A systematic review and meta-analysis were therefore undertaken to investigate continuation rates and reasons for discontinuation of IUDs currently available or comparable to those currently in use in the UK based on IUD type involving women aged under 30.

OBJECTIVES

To determine which currently available IUDs have higher continuation rates in nulliparous women aged under 30 by systematically reviewing published studies. Discontinuation rates and reasons for discontinuation were secondary outcomes.

METHODS

An appraisal of previous systematic reviews including publications by the Cochrane Collaboration Fertility Regulation Group, Faculty of Sexual and Reproductive Healthcare (FSRH) and National Institute for Health and Care Excellence (NICE) was performed. A search strategy was developed in conjunction with an Electronic Services Librarian. These informed the design of this systematic review and its protocol.

This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline (see supplementary material 1). Its protocol was registered on the International Prospective Register of Systematic Reviews database (PROSPERO; CRD42019120969, see supplementary material 2).[12] The protocol included an approach to consider other studies besides randomised controlled trials (RCTs) that report on IUD continuation if the RCTs determined eligible for inclusion in the systematic review were too few to address the review question.

Selection criteria

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved IUDs available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over 30, that involved IUDs not available, or not of the same design and size to those available, in the UK.

Where studies on IUDs currently available in the UK or only involving nulliparous women aged under 30 were lacking, studies with IUDs comparable in shape, size, total copper surface area or distribution on the IUD frame to those currently available in the UK, as well as with nulliparous women of all ages where those aged under 30 were involved, are included in this review.

Search Strategy

Nine electronic databases - the Allied and Complementary Medicine (AMED), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Nursing and Allied Health Professionals Database (EMCARE), Health Management Information Consortium (HMIC), General Medical Database (MEDLINE), Psychology and Allied Fields (PsychINFO), and PubMed – were searched using search terms (copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab from database inception to 7 February 2021 (updated to 11 May 2022). The following additional sources were searched using the term 'copper intrauterine': the Cochrane Library, Database of Abstracts and Reviews of Effects (DARE), Turning Research into Practice (TRIP) database, National Electronic Library of Health (merged with MEDLINE), Bandolier, Medicines and Healthcare products Regulatory Agency, FSRH, Royal College of Obstetricians and Gynaecologists, Department of Health, NICE, Scottish Intercollegiate Guidelines, and World Health Organisation websites. A Google Scholar search was also undertaken using the term 'copper intrauterine device young nulliparous'. The full search strategy is provided as a supplementary file (supplementary material 3).

Relevant articles published in English were identified by two authors and these exported into an Endnote library upon completion of searches. Following de-duplication, the relevant articles obtained from searches were exported to Rayyan, a web app for systematic reviews (rayyan.ai). In Rayyan, further de-duplication yielded unique entries of which abstracts, and then full texts, were screened independently by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. Additional citation screening of reference lists of both included and excluded studies was performed. Screening was initially done in batches of 20, then later increased to 50. Agreements were obtained between the first two authors and did not require a third review. Selected articles were RCTs and observational studies published in English involving IUDs available or comparable to those in the UK involving nulliparous participants aged under 30.

Quality Assessment and Data Summary

All articles selected for inclusion in the systematic review underwent a quality assessment using the Mixed Methods Appraisal Tool version 2018 (MMAT).[13] The MMAT risk of bias tool was chosen because it was applicable to all the study types of articles selected for inclusion. The highest possible total MMAT score conforming with best quality was seven, while the lowest possible score for poor quality was zero. Included articles were initially quality assessed by the two authors separately and then agreement reached.

Data extracted from articles included IUD type, study location(s) and year of publication, age of women, gravidity/parity of women, IUD continuation and discontinuation rates, and reasons for IUD discontinuation. Where a rate was not specified but could be reliably calculated, this was done to one decimal place. If a continuation rate was not specified, this was obtained by subtracting the discontinuation rate from 100, or adding all stated rates for reasons for discontinuation where these were mutually exclusive and subtracting from 100, if the report suggested such a calculation

to be valid. If a discontinuation rate was not specified, this was obtained by subtracting a stated continuation rate from 100, or by adding all stated rates for reasons for discontinuation where these were mutually exclusive, if the report suggested such a calculation was valid. Gross rates (obtained after excluding participants lost to follow up or removals to conceive) were used, except where only net cumulative rates were reported. Measurements were performed to obtain data from published graphs or figures where rates had been reported in this format but not numerically specified.

An Excel data collection form was developed, piloted with three articles selected for inclusion by one author, then revised and amended by the second author before proceeding to data extraction. Data from the 19 selected articles included in the review were extracted by one author unto the Excel spreadsheet and checked by the second author.

Data Analysis

Where available data were amenable to quantitative synthesis, random effects meta-analyses of proportions were performed using the metaprop suite of commands on STATA 16. Variances were stabilised using the Freeman-Tukey double arcsine transformation. This approach provides better approximation and results between 0% and 100% when synthesising proportions from small samples and multiple studies in meta-analyses.[14] Where possible, subgroup analysis was performed to examine differences between nulliparous women aged ≤30 years and nulliparous women of any age. Statistical heterogeneity was reported using I^2 and tau^2 statistics, since random effects meta-analyses was being performed. The I^2 value describes the percentage of the variability in effect estimates that is due to statistical heterogeneity (reflecting methodological diversity among the included studies) as opposed to chance. Conventionally, while an I^2 value <40% may not be significant, a value >50% may represent substantial heterogeneity and a value >75% may indicate considerable heterogeneity.[15] The tau^2 statistic measure of 'between-study variance', unlike the I^2 statistic, is not affected by size of included studies in a meta-analysis and hence may be considered more appropriate for estimating heterogeneity.[16] The effect of removing individual studies on the overall effect size (ES) was explored in sensitivity analyses (supplementary material 4). Publication bias was examined by producing Doi plots and generating LFK index values, considered a more appropriate measure of publication bias than funnel plots/Egger's test when performing meta-analyses of proportions.[17]

Patient and Public Involvement

The FSRH is the UK organisation committed to meeting the highest SRH standards, ensuring improvements in population SRH and supporting SRH professionals. The FSRH's Contraceptive Priority Setting Partnership in liaison with the James Lind Alliance yielded over 700 responses from patients, practitioners and the public that identified: 'Which interventions increase uptake and continuation of effective contraception including long-acting methods…?' as the top SRH research priority.[18] This influenced the research aims. IUD users attending a sexual health clinic over a four-week period were consulted about improving access to and use of intrauterine contraception. Their suggestions, which included studying women's experiences with IUDs, were used in developing the research question, aim, and study design. The Consumer Panel of the North East

Research Design Service was also consulted and the proposed research presented to them. The research plan was modified in line with their feedback.

Ethics Approval Statement

This study does not involve human participants and does not involve animal subjects. It was therefore exempt from Research Ethics Committee review.

RESULTS

Only one study, a prospective (non-RCT) cohort, provided information on an IUD available in the UK solely involving nulliparous users aged under 30.[19] This was inadequate to address the review question. As per the systematic review protocol, other studies on IUDs currently available in the UK or IUDs comparable to those available in the UK (Box 1) involving nulliparous women of all ages (so not limited to those aged under 30) were also screened. An IUD was considered comparable if at least two out of its four characteristics (copper surface area, shape/design, width and arms flexibility) were the same with IUDs currently used in the UK. So, for example, the Nova T200 was comparable because it has the same shape/design as a Nova T380, the same width as a Nova T380/Cu T380A/ TCu 380A and TT380 slimline, and the same flexible arms like a Nova T380. (Box 1)

Box 1 – Characteristics of IUDs in included studies

IUD brand / name	Copper (mm^2)	shape / design	width (mm)	arms' flexibility
Currently available in the UK				
Cu T380A / TCu 380A / TT380 Slimline	380	T with arm bands	>30	No
TCu 380A Nul / Mini TT380 slimline	380	T with arm bands	23.2	No
Multiload Cu 375	375	Ω	16 – 20.5	Yes, flex down
Nova T 380	380	T without arm bands	>30	Yes, flex up
Comparable to those available in the UK				
Nova T 200	200	T without arm bands	≥30	Yes, flex up
TCu 300	300	T without arm bands	>30	No
Cu T200 / TCu 200	200	T without arm bands	>30	No
TCu 220C	220	T without arm bands	>30	No

Thirty records were obtained upon this expansion and their full texts assessed. Eleven records were excluded for lack of usable outcome data (n=8; [5, 20-26]) and their full texts unobtainable (n=3; [27-29]) (see supplementary material 5). A total of 19 studies on IUDs available or comparable to those available in the UK, involving 13,045 nulliparous women, were eventually obtained and included in the systematic review (Table 1).[19, 30-47] Figure 1 depicts a PRISMA flow diagram detailing the search and selection process.[48]

Table 1 – Characteristics of Included Studies

Study / Authors	Year	Country	Study Design	Study Objectives	IUDs in study	Quality (MMAT score)
Abraham et al [19]	2015	USA	Prospective cohort	Relationship among young age, nulliparity, and continuation of long-acting reversible contraceptives	Copper T380A	Good (7)
Akintomide et al [30]	2019	UK	Retrospective records review	Discontinuation rates and reasons for discontinuation at 1 year of the small-sized Mini TT380 Slimline IUD compared with the standard-sized TT380 Slimline	Mini TT380 slimline TT380 slimline	Good (6)
Allonen et al [31]	1980	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 2 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (6)
Elkhateeb et al [32]	2020	Egypt	Prospective cohort	Acceptability of IUD use in nulliparous women by both women and health care providers	Copper T380A	Good (7)
Fugere [33]	1990	Canada	Prospective cohort	Clinical performance of the Nova T200 IUD over 5 years	Nova T200	Good (7)
Hall and Kutler [34]	2016	USA	Prospective cohort	Experience and satisfaction of nulliparous intrauterine contraception users at 1, 6, 12 and 18 months	Copper T380A	Good (7)
Kaislasuo et al [35]	2015	Finland	Prospective cohort	Menstrual characteristics and ultrasonographic uterine cavity measurements predict bleeding and pain in nulligravid women using intrauterine contraception	Nova T380	Good (7)
Larsen et al [36]	1981	Denmark	RCT – patient blind	Comparison of clinical performances of Progestasert and Copper T200 at 12 months	Copper T200	Good (5)
Lewit [37]	1973	USA	Prospective cohort	Two years' experience of the Copper T200	Copper T200	Good (7)
Liedholm and Sjoberg [38]	1974	Sweden	Prospective cohort	Two years' experience with the Copper T200 and comparison between nulliparous and parous women	Copper T200	Good (7)
Luukkainen et al [39]	1979	Denmark, Finland Sweden	RCT – double blind	Experience and clinical performance of the Nova T200 and Copper T200 at 12 months	Nova T200 Copper T200	Good (6)
Luukkainen et al [40]	1987	Denmark, Finland, Hungary, Norway, Sweden	RCT – no blinding	Use-effectiveness and clinical performance of levonorgestrel- and copper-releasing intrauterine devices at 12 months	Nova T200	Good (6)
Mishell et al [41]	1973	USA	Prospective cohort	Continuation and clinical performance of TCu 200 in nulliparous women	Copper T200	Good (7)
Nygren et al [42]	1981	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 3 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (7)

Ostergard and Gunning [43]	1979	USA	RCT – blinding not stated	Continuation and clinical performances of Copper T200 and Dalkon Shield in nulligravid women at 12 months	Copper T200	Good (5)
Otero-Flores et al [44]	2003	Mexico	RCT – single (patient) blind	Comparison of clinical performance of three different IUDs in nulliparous women	Copper T380A Copper T380A Nul Multiload 375 sl	Good (6)
Roy et al [45]	1974	USA	Prospective cohort	Experience with three different IUD models in nulliparous women at 1 year	Copper T380A Copper T300 Copper T200	Good (7)
Sivin and Stern [46]	1979	USA	RCT – double blind	Experience of three different IUDs in nulliparous and parous women	Copper T380A Copper T220C Copper T200	Good (5)
Timonen et al [47]	1974	Finland	Prospective, single (patient) blind	Use-effectiveness of Copper T300 at 1 year	Copper T300	Good (7)

All included studies were generally of good quality (mean 6.42 [5-7]; see supplementary material 6 for quality and risk of bias assessments). The lowest MMAT score of five obtained was for three RCTs published in 1979 and 1981, possibly related to inadequate reporting.[36, 43, 46] Their reports did not confirm that randomisation had been appropriately performed, [36, 46] randomised groups were comparable at baseline, [43, 46] nor that outcome assessors were blinded to the intervention provided [36, 43].

Although the outcome data obtained were considered homogenous, studies' designs, participant ages and parity, and IUD types were not; making a quantitative synthesis of the outcome data in totality inappropriate. Results were therefore grouped into three to include studies involving: 1. IUD types currently available in the UK and only nulliparous women aged ≤30; 2. IUD types currently available in the UK and nulliparous women of all ages; 3. IUD types comparable to those available in the UK and nulliparous women of all ages. (Table 2) Estimated continuation rates at 12 months of IUD types from included studies obtained from data amenable to synthesis is reported in Table 3, while tau^2 values for heterogeneity of included studies is provided separately (see supplementary material 7).

Table 2 – Summary of Findings

Study	IUD types (N[µ])	Age at insertion (y)	Study period	Continuation rates % (n)[CI]	Discontinuation rates % (n)	Removal for bleeding/pain % (n)	Expulsion % (n)	Pregnancy % (n)
Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30								
RCT								
Otero-Flores et al 2003 [44] [µ §]	TCu 380A (375) TCu 380A Nul (367) ML Cu 375 sl (374)	23.2±6.8 22.4±6.6 22.6±6.4	12 months	30.7 (115) 91.3 (335) 89.0 (333)	69.3 (260) 8.7 (32) 11.0 (41)	61.6 (231) 3.81 (14) 6.68 (25)	3.47 (13) 1.91 (7) 1.87 (7)	1.07 (4) 0.54 (2) 0.00 (0)
Non-RCT								
Abraham et al 2015 [19]	Cu T380A (201) Cu T380A (44) Cu T380A (201) Cu T380A (44)	20 - 25 <20 20 - 25 <20	12 months 24 months	82 [76-87] 79 [64-89] 73 [66-79] 64 [48-77]	ns ns	ns ns	ns ns	ns ns
Hall and Kutler 2016 [34]	Cu T 380A (21)	18 - 30	12 months	73.7 (14)	26.3 (5)	10.5 (2)	10.5 (2)	5.26 (1)
Studies of IUD types currently available in the UK involving nulliparous women of all ages								
RCTs								
Sivin and Stern 1979 [46][¶,a]	TCu 380A (2254) TCu 220C (1301) TCu 200 (4215)	<20 - 35+ <20 - 35+ <20 - 35+	2y	55.7 57.8 54.2	44.3 42.2 45.8	21.9 19.5 16.8	7.8 9.8 9.8	0.8 1.6 5.1
Non-RCTs								
Akintomide et al 2019 [30]	TT380 Slimline (27) Mini TT380 Slimline (53)	15 – 37 16 - 37	1y	66.7 (18) 86.8 (46)	33.3 (9) 13.2 (7)	ns ns	3.7 (1) 3.77 (2)	0 (0) 0 (0)
Elkhateeb et al 2020	TCu 380A (90)	16 - >30	6 months	94.4 (85)	5.6 (5)	ns	0 (0)	ns

[32]								
Kaislasuo et al 2015 [35]§	Nova T380 (42)	18 - 43	1y	83.3 (35)	16.7 (7)	ns	4.76 (2)	ns
Roy et al 1974 [45]	TCu 380A (785) TCu 300 (347) TCu 200 (472)	<14 - >33 15 - >33 <14 - >33	12 months	81.9 80.7 74.2	18.1 19.3 25.8	9.1 9.2 10.7	3.8 6.1 5.4	0.2 0.6 1.7
Studies of IUD types comparable to those available in the UK involving nulliparous women of all ages								
RCTs								
Luukkainen et al 1979 [39][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	12 months	ns ns	ns ns	15.3 23.4	6 10.8	0.53 2.3
Allonen et al 1980 [31][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	24 months	ns ns	ns ns	23.5 24	6.5 14	1.14 5.28
Nygren et al 1981 [42][a]	Nova T200 (ns) Cu T200 (ns)	<20 - >35	36 months	36.9 31.0	ns ns	28.3 (74) 28.2 (68)	10.3 (27) 10.7 (26)	1.5 (4) 6.5 (15)
Larsen et al 1981 [36][a]	Cu T200 (99)	15 - 44	12 months	73	27[α]	16	5	1
Luukkainen et al 1987 [40]	Nova T200 (77)	17 – 40	12 months	73.1	26.9[α]	10.4	9.2	0
Ostergard and Gunning 1979 [43]	TCu 200 (117) TCu 200 (115)	18 – 34	6 months 12 months	88.9 (104) 73.0 (84)	11.1 (13) 27.0 (31)	6.0 (7) 12.2 (14)	3.41 (4) 6.09 (7)	0 (0) 0 (0)
Non-RCTs								
Fugere 1990 [33]	Nova T200 (54)	17 - 42	24 months	ns	ns	17.2	1.9	0
Lewit 1973 [37]	TCu-200 (2099) Nulligravid subgroup: TCu-200 (1585)§ Age subgroups: TCu-200 (1130) TCu-200 (2468) TCu-200 (1513)	15-49 15-49 15 – 19 20 – 24 25 – 29	1y 1y 1y 1y 1y	73.3 75.9 67.3 73.8 77.6	26.7 24.1 32.7 26.2 22.4	9.4 9.6 7 8.3 5.8	10.7 8.7 15 8.5 8.7	1.3 0.8 2.3 2.8 1.5

	TCu-200 (683) TCu-200 (449)	30 – 34 35 - 49	1y 1y	81.7 85.2	18.3 14.8	7.9 6.8	6 3.1	0.4 0.3
Liedholm and Sjoberg 1974 [38]	T-Cu 200 (208) `	14 - 40	12 months 24 months	70.2 60.3	29.8 39.7	18.1 28	0.5 0.5	2.9 (6) 2.9 (6)
Mishell et al 1973 [41][a]	TCu 200 (471)	14-33	3 months 6 months 12 months	92.6 84.5 74.2	7.4 15.5 25.8	2.8 5.8 10.7	2.6 4.7 5.4	0.2 0.4 1.7
Timonen et al 1974 [47]	T Cu-300 (138)	<25 - 40+	12 months	84.7	15.3	7.2	1.6	1.6

RCT – randomised controlled trial; ns – not stated; μ - sample size or participants excluding those lost to follow up or removals to plan pregnancy; § - nulligravid women only; ¶ - a combination of double blind studies; α – not stated; obtained by subtraction of continuation rate from 100; a – net cumulative rates; b – data obtained from graphs or figures

Table 3 – Estimated continuation rates at 12 months of IUD types from included studies

	Continuation rates with numbers of patients (*n*), and statistical heterogeneity (tau² and I²) values [of studies included in subgroup]		
IUD type	**Nulliparous women aged <30**	**Nulliparous women of any age**	**Overall effect size (all studies)**
TCu 380A[a]	81.60% (95% CI 76.52-86.21%)[b] (*n*=264; tau²=0.0; I^2= .%, p= .) [19, 34]	80.97% (95% CI 76.04-85.48%) (*n*=971; tau²=0.005; I^2= .%, p= .) [19, 30, 45]	81.93% (95% CI 79.66-84.09%) (*n*=1235; tau²=0.0; I^2=0.00%, p=0.47)[19, 30, 34, 45]
Smaller TCu 380A[c]	not applicable – only one study group	91.02% (95% CI 88.01-93.64%) (*n*=420; tau²=0.0; I^2=0.00%, p= .) [30, 44]	91.02% (95% CI 88.01- 93.64%) (*n*=420; tau²=0.0; I^2=0.00%, p= .) [30, 44]
TCu 300	not applicable – no study	81.92% (95% CI 78.35-85.24%) (*n*=485; tau²=0.0; I^2=0.00%, p= .) [45, 47]	81.92% (95% CI 78.35-85.24%) (*n*=485; tau²=0.0; I^2=0.00%, p= .) [45, 47]
TCu 200	73.03% (95% CI 67.63-78.10%) (*n*=5111; tau²=0.010; I^2= .%, p= .) [37]	76.51% (95% CI 72.67-80.14%) (*n*=3277; tau²=0.012; I^2=82.97%, p=0.00) [37-39, 41, 43, 45]	75.44% (95% CI 72.32-78.43%) (*n*=8388; tau²=0.012; I^2=89.17%, p=0.00) [37-39, 41, 43, 45]
Nova T200	not applicable – no study	73.21% (95% CI 70.10-76.22%) (*n*=818; tau²=0.0; I^2=0.00%, p= .) [39, 40]	73.21% (95% CI 70.10-76.22%) (*n*=818; tau²=0.0; I^2=0.00%, p= .) [39, 40]

a – excludes Otero-Flores et al study data; b – includes women aged 30 from Hall and Kutler study data; c – TCu 380A Nul/Mini TT380 Slimline IUDs

Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30

Three studies - Abraham et al (2015), Hall and Kutler (2016) and Otero-Flores et al (2003) - reported on IUDs in women aged ≤30 involving the Copper T380A IUD (TCu 380A or Cu T380A).[19, 34, 44] The TCu 380A data obtained from Otero-Flores et al (2003) was an outlier, with 30.7% reported as continuation at 12 months[44]. This was much lower than for the other two studies with a pooled estimate of 81.60% (95% CI 76.52-86.21%).[19, 34] (Figure 2) When the Otero-Flores et al data were included in this TCu 380A meta-analysis, nulliparous women ≤30 years of age at 12 months had a continuation rate of 66.98% [95% CI 32.09-93.90%]. (Figure 3)

Continuation was also higher with age at 12 and 24 months when nulliparous TCu 380A IUD users aged <20 and 20 - 25 were compared (Table 2).[19]

Studies of IUD types currently available in the UK involving nulliparous women of all ages

Five studies reporting data pertaining to seven population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the TCu 380A IUD at 12 months post insertion.[19, 30, 34, 44, 45] The pooled estimated continuation rate of the Copper T380A IUD type in nulliparous women of all ages from four studies was 81.93% (95% CI 79.66-84.09%).[19, 30, 34, 45]. Additionally, statistical heterogeneity was found to be low/absent but was not statistically significant ($tau^2 = 0.0$, $I^2 = 0.00\%$, $p = 0.47$). Sensitivity analysis confirmed that the overall effect size was largely robust to the exclusion of individual studies (-1.01% to +0.21% change in effect size, see supplementary material 4).

The estimated TCu 380A continuation rate was still good at 71.65% (95% CI 51.15-88.44%; $tau^2 = 0.299$, $I^2 = 98.21\%$, $p = 0.00$) when the Otero-Flores et al data was included.[44] (Figure 3). An LFK index value of 6.77 identified major Doi plot asymmetry consistent with publication bias (see supplementary material 8).

Individual studies showed the TCu 380A had higher discontinuation related to bleeding/pain and expulsion [34, 44, 46] when compared to IUDs of smaller size or those with flexible arms [30, 44](Table 2).

The highest continuation rates at 12 months were reported with smaller-sized IUDs - the Copper 380A Nul (TCu 380A Nul - 91.3%), Multiload Copper 375 sl (ML Cu 375 sl - 89%), and Mini TT380 slimline (86.8%)(Table 2). These data were obtained from only two studies whose participants were aged 15 to 37.[30, 44] Meta-analysis of continuation rate data on the TCu 380A Nul/Mini TT380 slimline IUD type gave a weighted average of 91.02% (95% CI 88.01-93.64%) (Figure 4). These smaller IUDs were also associated with the lowest rates of removals for bleeding/pain (3.80 – 6.68%) and expulsion (1.87 – 3.77%) reported in nulliparous women at 12 months (Table 2).

STUDIES of IUD types comparable to those in the UK involving nulliparous women of all ages

Two studies reporting data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T300 IUD (TCu 300) at 12 months post insertion [45, 47], reporting an overall effect size of 81.9% (95% CI 78.35-85.24%, see figure 5).

Seven studies reporting data pertaining to 11 population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T200 IUD (TCu 200 or Cu T200) at 12 months post insertion, with a weighted average of 75.44% (95% CI 72.32-78.43%, see figure 6).[36-38, 40, 41, 43, 45] These were also amenable to meta-analysis examining the proportion of women discontinuing the TCu 200 at 12 months post insertion due to bleeding and/or pain, expulsion and pregnancy (see supplementary material 9). For these meta-analyses, nulliparous women aged <30 years compared to nulliparous women of any age at 12 months were found to be less likely to continue to use the TCu 200 (73.03% [95% CI 67.63-78.10%] versus

76.51% [95% CI 72.67-80.14%]) and discontinue the TCu 200 due to bleeding and/or pain (7.05% [95% CI 5.59-8.65%] versus 12.77% [95% CI 8.48-17.78%]). Nulliparous women aged <30 years compared to nulliparous women of any age at 12 months were however more likely to discontinue the TCu 200 due to expulsion (10.52% [95% CI 7.17-14.41%] versus 4.93% [95% CI 2.93-7.39%]) and pregnancy (2.19% [95% CI 1.47-3.05%] versus 1.15% [95% CI 0.54-1.95%]). The overlapping confidence intervals for these two effect sizes suggest the difference in effect is not statistically signficant, and therefore may or may not be clinically significant. Statistical heterogeneity values for overall TCu 200 continuation rates as well as discontinuation rates for bleeding/pain and expulsion were - $tau^2 = 0.012$, $I^{\wedge 2} = 89.17\%$, $p = 0.00$; $tau^2 = 0.025$ $I^{\wedge 2} = 94.59\%$, $p = 0.00$; and $tau^2 = 0.018$, $I^{\wedge 2} = 92.58\%$, $p = 0.00$ respectively (see figure 6 and supplementary material 9). Sensitivity analyses confirmed that the overall effect sizes were largely robust to the exclusion of individual studies (see supplementary material 4). In all cases, their LFK index values identified major Doi plot asymmetry consistent with publication bias (see supplementary material 8).

Continuation was seen to progressively improve with age where Lewit (1973) reported rates in nulliparous TCu 200 users by age groups 15 – 19, 20 – 24, 25 – 29, 30 – 34, and 35 – 49.[37] (Table 2)

Two studies reported data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Nova T200 at 12 months post insertion,[39, 40] reporting a weighted average of 73.21% (95% CI 70.10-76.22%, see figure 7).

Studies also showed IUDs with flexible arms (Nova T, Multiload)[31, 39, 44] were associated with higher continuation and lower removal rates for bleeding/pain, expulsion and pregnancy where compared to IUDs with rigid arms (Cu T or TCu). (Table 2).

DISCUSSION

Findings and Interpretation

Evidence on IUDs currently used in nulliparous women aged under 30 is limited. These findings estimate the continuation rate for the recommended TCu 380A IUD [11] to be 81% at 12 months post insertion based on four studies involving young nulliparous women.[19, 30, 34, 45] This was the same estimate for the TCu 300 based on two studies.[45, 47] Smaller sized and flexible IUDs had higher continuation rates of 86-91% in this group of women based on two studies as well as fewer removals for bleeding/pain and expulsion compared to the TCu 380A or IUDs of same rigid design or size.[30, 44] Lower continuation rates of 75% and 73% were obtained for the TCu T200 and Nova T200 based on eight studies.[36-41, 43, 45]

The study by Otero-Flores et al was the only reported RCT at 12 months to solely involving IUDs currently used in the UK and nulliparous women aged ≤30.[44] Over a thousand nulliparous women aged 15 to 30 were randomised to receive three different IUDs - TCu 380A (width 32mm), TCu 380A Nul (width 23mm) and ML Cu 375 sl (width ≤20mm), the latter two of which were primarily designed for nulliparous women. The TCu 380A rates of discontinuation (69.3%) and bleeding/pain as reasons for discontinuation (61.6%) were significantly higher than for TCu 380A Nul (8.7% and 3.81%) and ML Cu 375 sl (11.0% and 6.68%), as well as significantly different from rates reported by other included studies involving the TCu 380A. This could be because the TCu

380A considerably differs in size from the TCu 380A Nul and ML Cu 375 sl IUDs, and Otero-Flores et al also exclusively involved nulligravid participants (as opposed to nulliparous).

Sivin and Stern (1979) was the only other RCT involving a TCu 380A that reported separately on nulliparous users.[46] However, their TCu 380A discontinuation and bleeding/pain rates, 44.3% and 21.9% respectively, were obtained at two years and their participants aged <20 to 35+.

The disparity in discontinuation rates reported by Otero-Flores et al [44] and Sivin and Stern [46], in addition to criticism for inaccuracies, have suggested that the findings by Otero-Flores et al may be unreliable. But it may in fact be inappropriate to directly compare other studies' TCu 380A data, including that of Sivin and Stern, to Otero-Flores et al's data. Study design as well as participants' ages, gravidity/parity, environments and reported use duration were not the same. Otero-Flores et al participants were younger (≤30 years), exclusively nulligravid, 'highly educated' and based in a Mexico city with free access to healthcare in the millenial era, with the study being single-(patient) blinded. This contrasts with most studies involving the TCu 380A or similar IUDs where participants were more likely to be aged 30 or older, parous, with unspecified educational attainment. The Sivin and Stern study population were living and accessing healthcare (which was not stated to have been free) across the United States in the late 1970s (over two decades earlier than the Otero-Flores study, and not long after the Dalkon Shield era), with the study being double-blinded. Other explanations for disparity could be that modern younger nulligravids may be less tolerant of IUD unwanted effects, and that some contraceptive research may be less likely to acknowledge participants' reasons and wishes for early IUD discontinuation.[49]

The TCu 200 IUD was ≥33mm in width and/or height so perhaps larger than a standard-sized TCu 380A.[50] IUD size may contribute to pain, which may explain TCu 200's lower continuation rates compared to the TCu 380A. However the TCu 300, of same design and size as the TCu 200,[47] unexpectedly had a higher continuation rate than the TCu 200. This is because higher copper content has been associated with more bleeding which contributes to early discontinuation.[51] The TCu 300 data were limited to two studies that both had total MMAT scores of 7,[45, 47] whereas the TCu 200 data had been obtained from seven studies with MMAT scores of 7,[37, 38, 41, 45] 6,[39] and 5[43] respectively.

Strengths and Limitations

This is the first systematic review to explore IUD types in younger aged nulliparous women. It has included all observational studies that provided information on IUD continuation or reasons for discontinuation in this user group. Non-restriction to RCTs may be considered a limitation, but a realist approach of expanding the inclusion criteria where RCT evidence is lacking could be commendable and more representative of routine practice. Using the MMAT, the quality of reviewed and included studies in this systematic review was good overall.

Articles for inclusion were unfortunately limited to publications in the English language. The absence of studies on IUDs currently available in the UK solely involving women aged under 30 warranted including all ages if women under 30 years were involved, and up to (≤) 30 years for the TCu 380A data and meta-analysis because of the ages of the Hall and Kutler study participants (18-30 years). Many studies did not report all the required information hence some included studies had missing information (Table 2). Most studies did not differentiate between nulligravid and nulliparous participants, many age ranges were not specific (e.g. ≤19 - ≥35), while some reports

e.g. Sivin and Stern (1979) were of a combination of individual studies [46]. Similarly, it appeared common for older studies to only state numbers (rather than rates or percentages) or only graphically depict data on continuation or unwanted effects. It is also not unusual for a systematic review, e.g. Hubacher (2007), including such studies to calculate or measure accordingly as has been done in this review.[7] These potential limitations and all mitigating actions taken have been appropriately stated and are not considered to impact the validity of the review.

Relevance of Findings

IUD use in young nulliparous women has been established to be safe, effective and acceptable.[52-54] It is recommended that women are provided the most appropriate IUD types for their uterine cavity size, with their uterine cavity width (measurable using a cavimeter or ultrasonography, not routinely practised) rather than length (routinely measured using a hysterome) influencing IUD type choice.[29, 55-57] This systematic review emphasises this provision recommendation warrants further research and suggests which IUD types may be more suitable for younger aged nulliparous women.

Recommendations

Strengthening evidence for contraceptive choice and continuation is needed to improve sexual health in younger aged women. Prospective observational studies that include various IUD designs and types, and detailed reporting of users' experiences could facilitate a better understanding of early IUD discontinuation and reasons for discontinuation based on IUD types. Studies designed to overcome the challenges of recruiting large numbers from varied demographic backgrounds, significant loss to follow up, and time or funding constraints are also likely to yield data widely applicable to IUC provision in and outside the UK.

CONCLUSION

Research is lacking on outcomes with the IUD types currently in use by young nulliparous women in the UK. Available evidence estimates a continuation rate of 81% at 12 months for the recommended standard-sized TCu 380A IUD in these women. More studies are needed to better estimate continuation rates for smaller-sized and flexible IUDs which may be higher in this user group. This in turn will help to improve sexual health in these women.

FIGURES

Figure 1 – PRISMA Flow Diagram

Figure 2 - TCu 380A continuation rates (excl Otero-Flores et al)

Figure 3 - TCu 380A continuation rates (incl Otero-Flores et al)

Figure 4 - Smaller TCu 380A continuation rates

Figure 5 - TCu 300 continuation rates

Figure 6 - TCu 200 continuation rates

Figure 7 – Nova T200 continuation rates

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The authors report no conflict of interest.

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No additional data available.

AUTHOR CONTRIBUTIONS

HA: research idea, study design, protocol, searches, first reviewer, data summary, writing - original draft, funding application for open access publishing, project administration; AJ: second reviewer, supervision, writing – review and editing, project administration; PB: searches, writing – review and editing; MM: meta-analysis, writing – original draft, review and editing; JR: contributed to research idea, study design, protocol, funding applications, and project administration, as well as supervision and writing – review and editing. All authors approved the final version.

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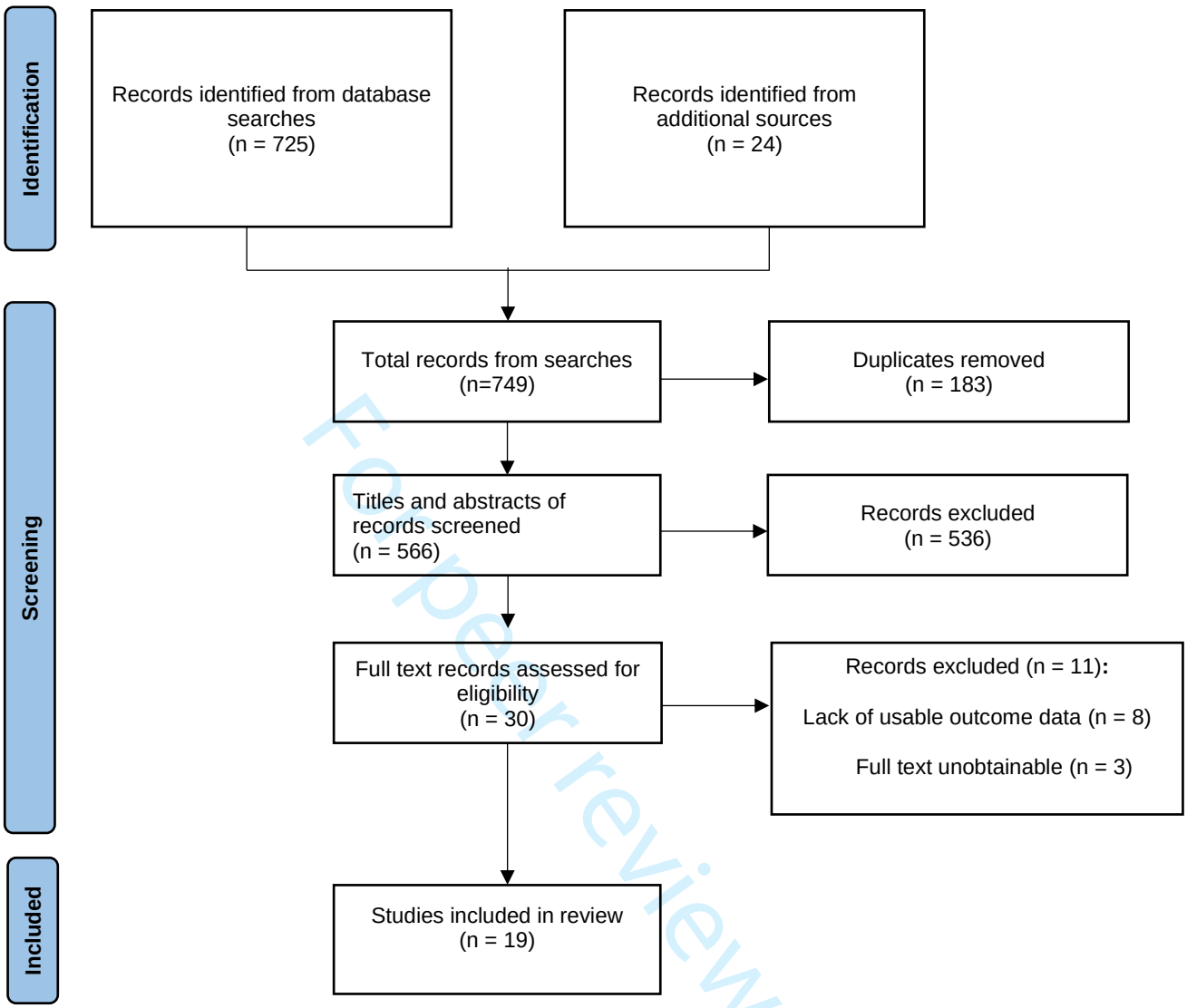
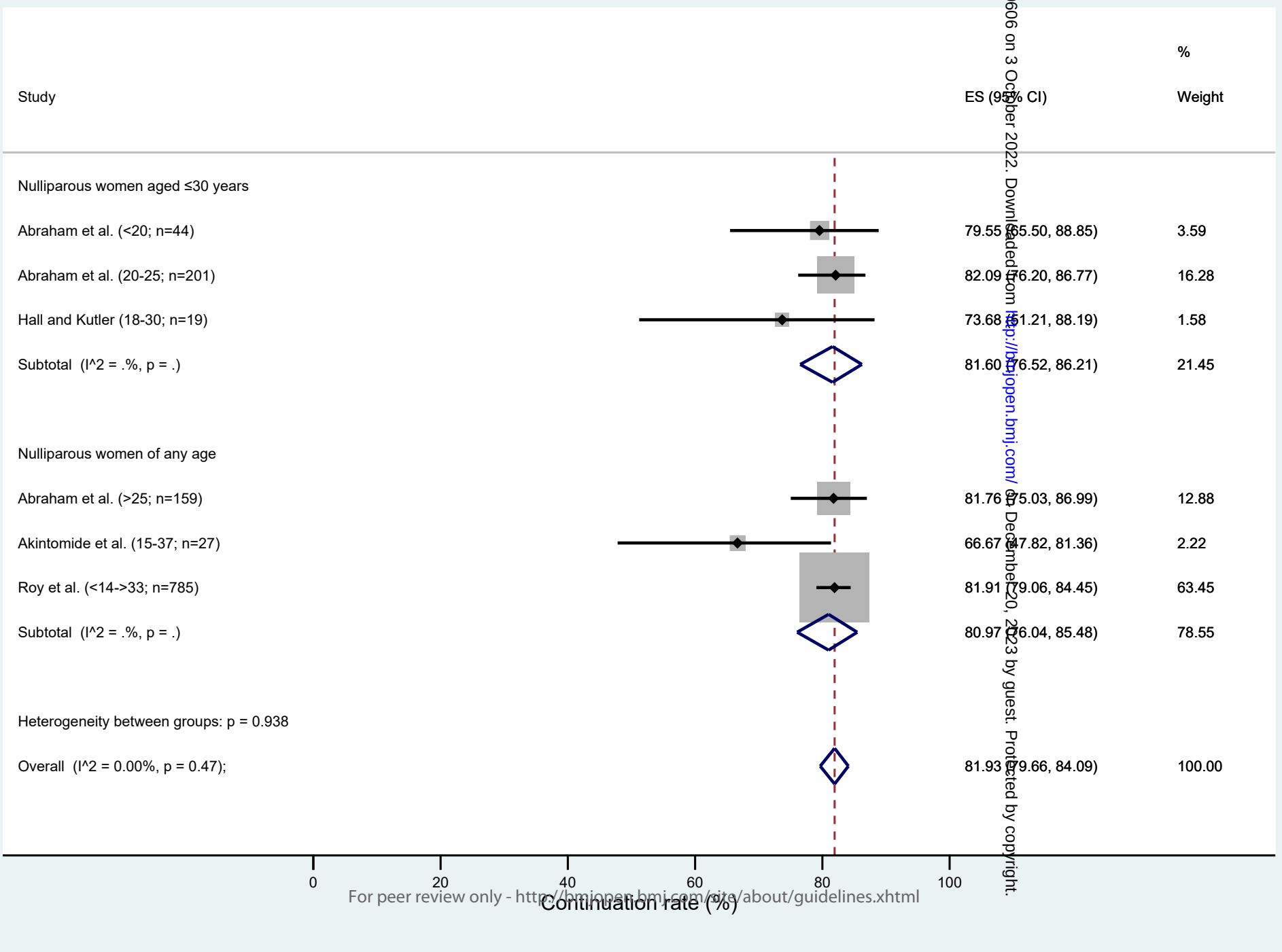
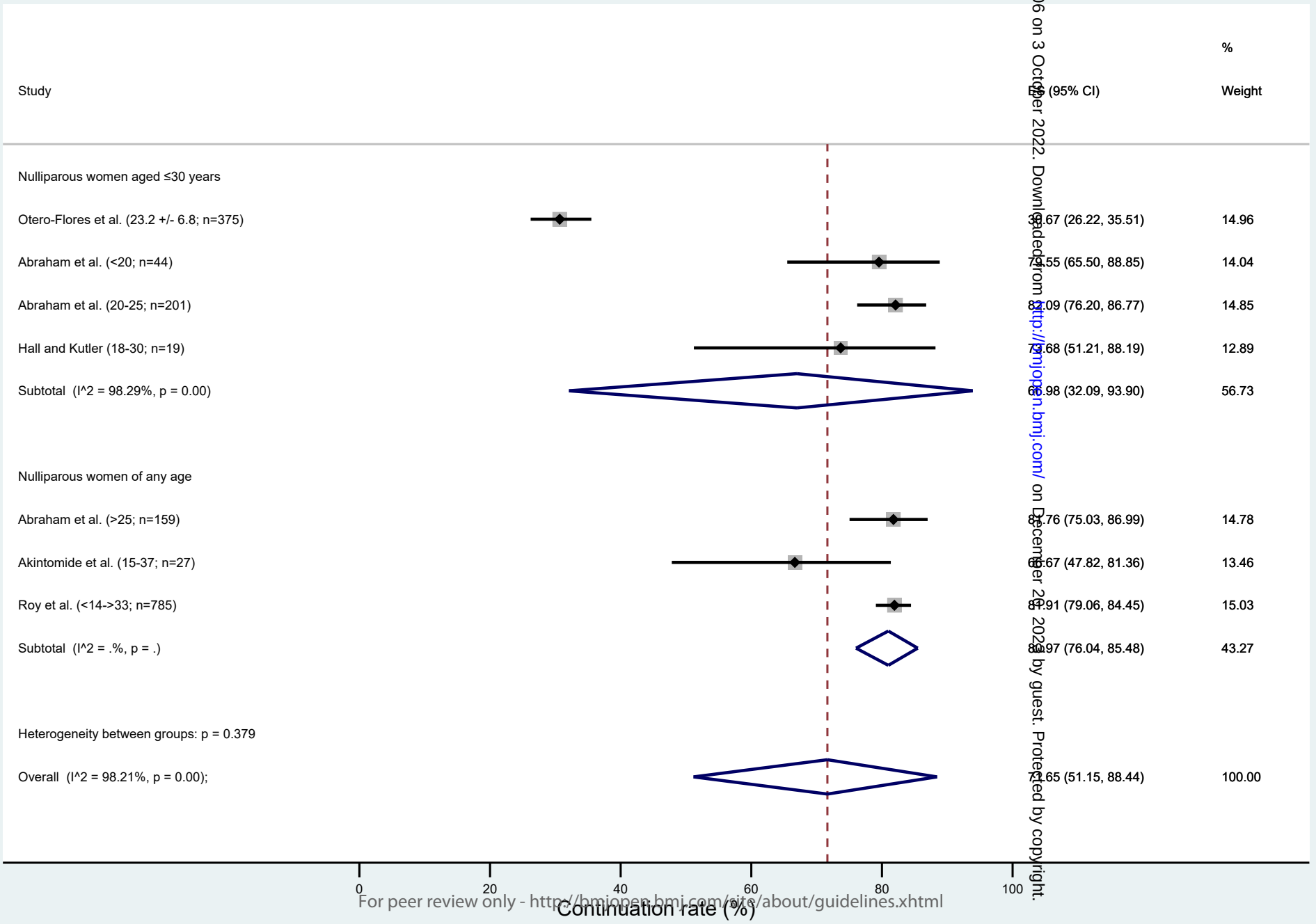


Figure 1 – PRISMA 2020 flow diagram of searches and selection of studies

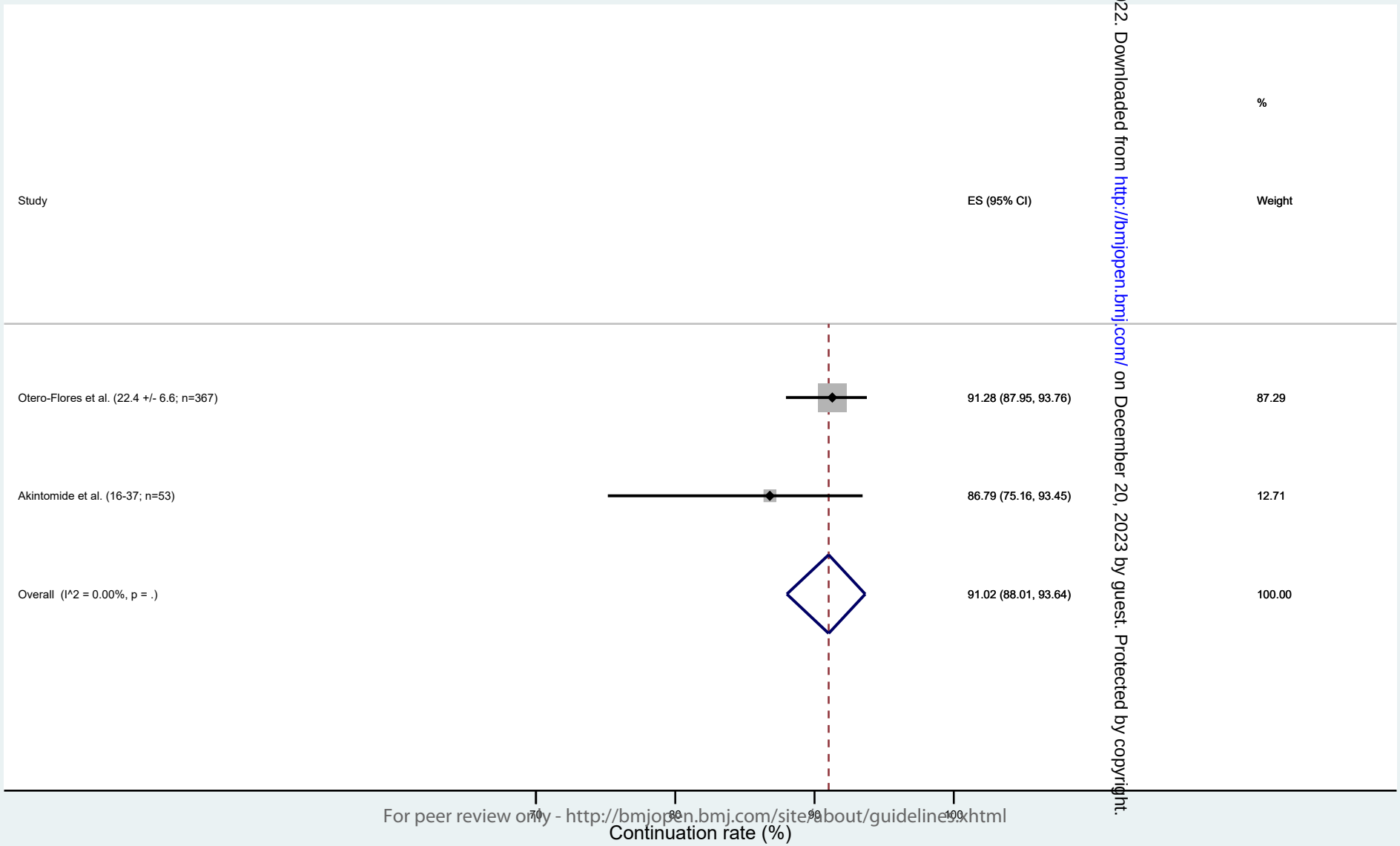
TCu 380A continuation rate at 12 months post-insertion (excl. Otero-Flores)



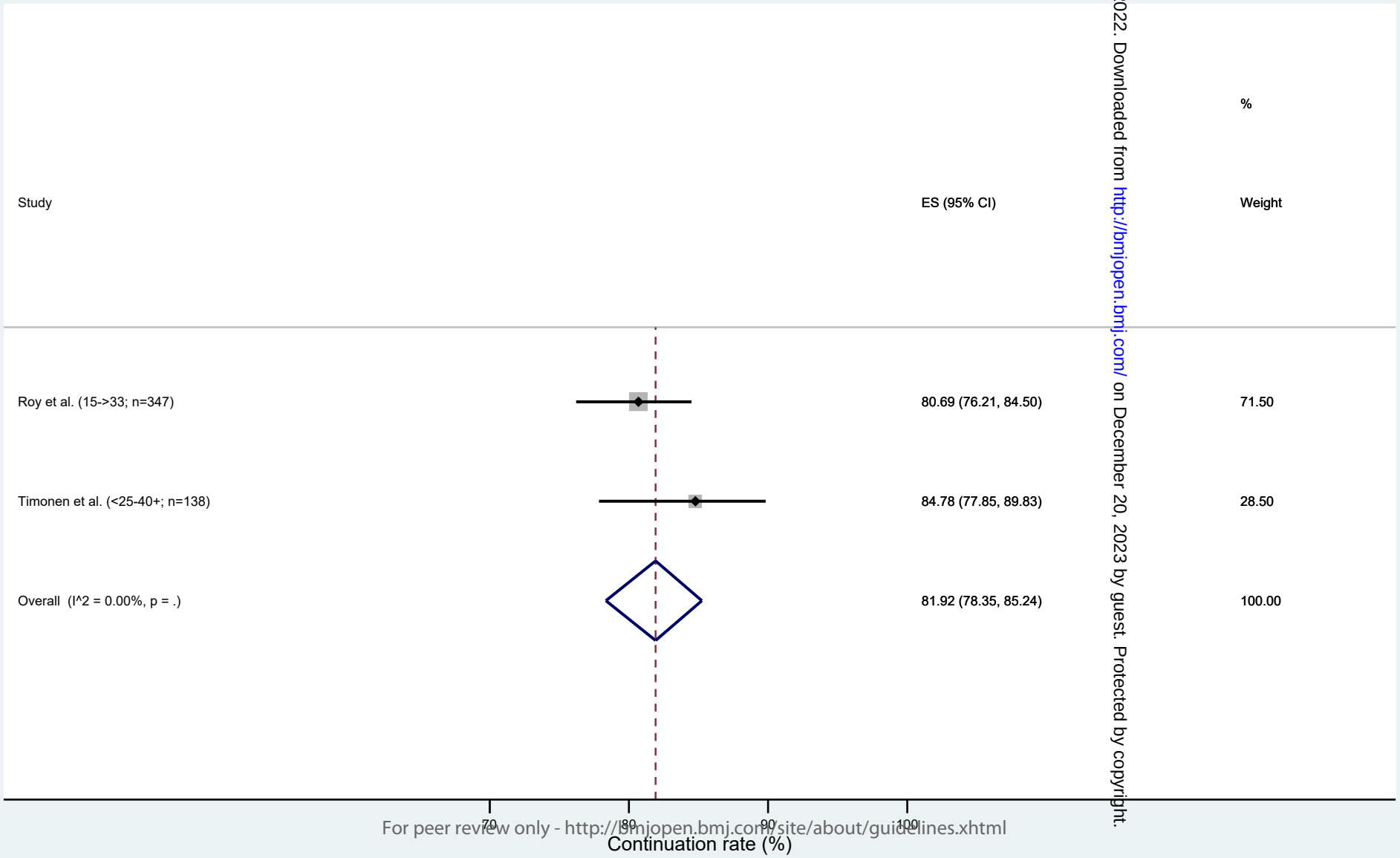
TCu 380A continuation rate at 12 months post-insertion (incl. Otero-Flores)



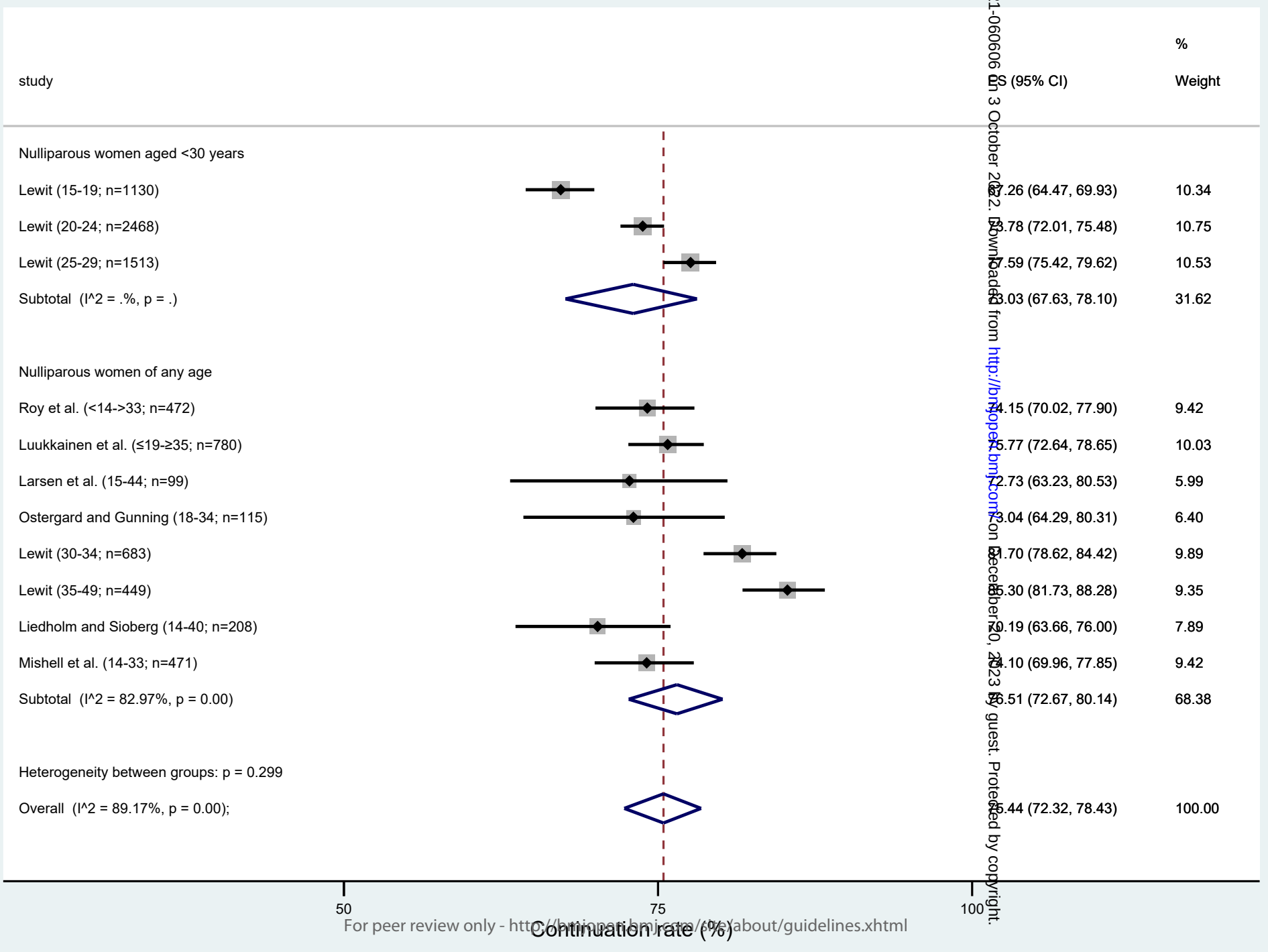
Smaller TCu 380A continuation rate at 12 months post-insertion



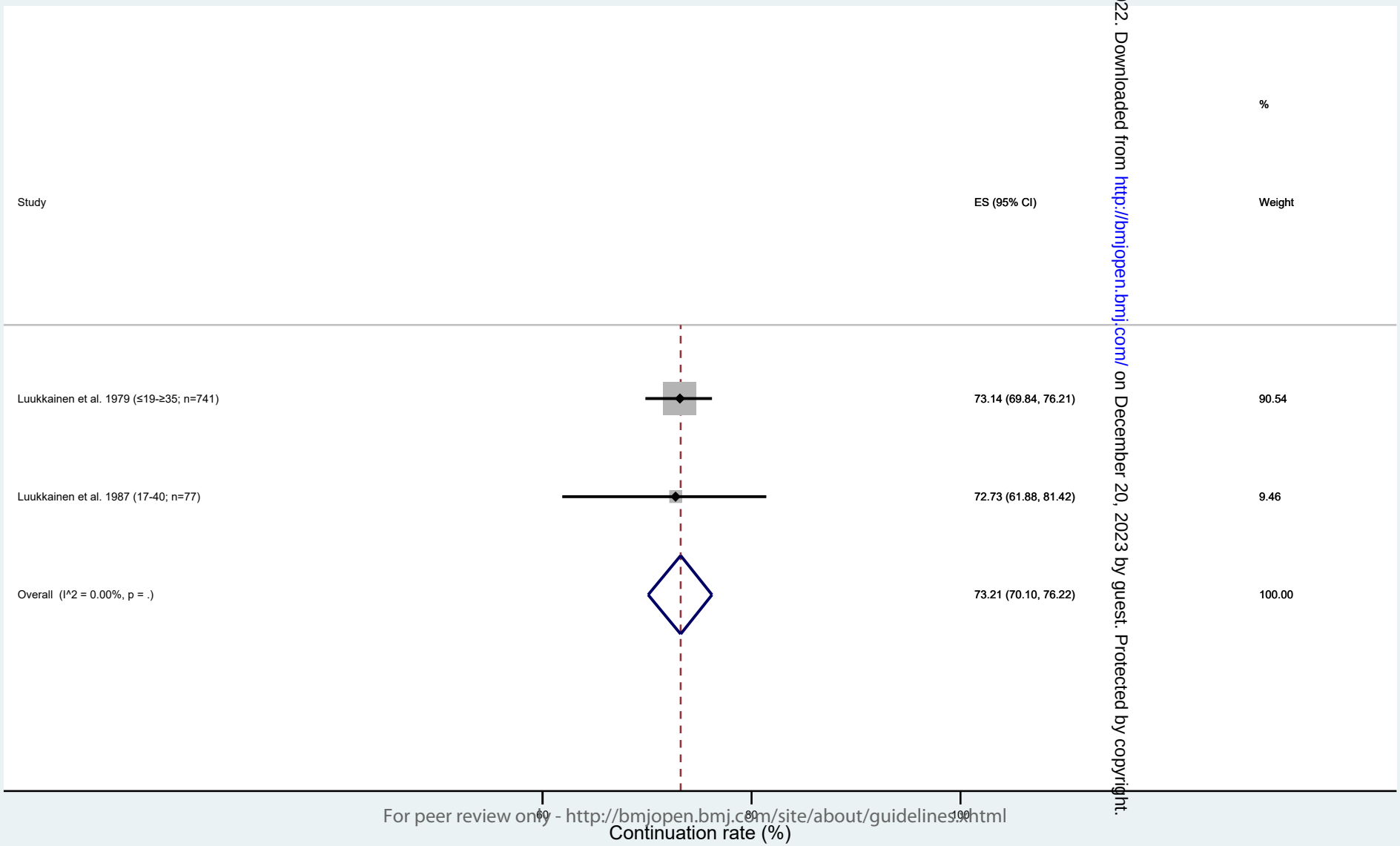
TCu 300 continuation rate at 12 months post-insertion



TCu 200 continuation rate at 12 months post-insertion



Nova T200 continuation rate at 12 months post-insertion



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6 Supplementary material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 6-7 Supplementary material
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 6-7 Supplementary material
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6-7 Supplementary material
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7 Supplementary material
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7 Supplementary material
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 6-7 Supplementary material
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 6-7 Supplementary material
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7 Supplementary material

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 6-7 Supplementary material
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 6-7 Supplementary material
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 6-7 Supplementary material
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 6-7 Supplementary material
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 8-13 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 10 Supplementary material
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 13-9 Table 2-3 Figures 2 – 7 Supplementary material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 16-9 Figures 2 – 7 Supplementary material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 16-9 Figures 2–7 Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 16-9 Figures 2–7 Supplementary material
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 16-9 Figures 2–7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 19-20
	23b	Discuss any limitations of the evidence included in the review.	Page 19-20
	23c	Discuss any limitations of the review processes used.	Page 20
	23d	Discuss implications of the results for practice, policy, and future research.	Page 21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5 Supplementary material
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplementary material
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pages 5 and 8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 22
Competing interests	26	Declare any competing interests of review authors.	Page 22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Copper intrauterine contraception discontinuation in nulliparous and young women

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin

Citation

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Review question

Which copper intrauterine devices are associated with higher discontinuation rates in young and nulliparous women?

Searches

Databases [including the Cochrane Library, the Database of Abstracts and Reviews of Effects (DARE), MEDLINE (Ovid), Excerpta Medica Database (EMBASE), Turning Research into Practice (TRIP) database and National Electronic Library of Health] and relevant websites [including Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, Medical Defence Unions, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar] will be searched using MeSH terms combined with key words for relevant articles published from 1966 to date. Reference lists of relevant articles will also be searched to identify more articles. The full texts of relevant articles will be screened, duplicates excluded and then data from selected articles included in the review.

Randomised controlled trials (RCTs) involving copper intrauterine devices (IUDs) available or comparable to those in the UK published in English will be included. Other studies that report on the main outcome (observational and qualitative studies) will be included and/or summarised if the number of RCTs eligible for inclusion are too few to answer the review question.

Key words

Copper intrauterine device related: copper intrauterine device, copper intrauterine contraceptive device, copper intrauterine contraception, copper coil, IUD

Nulliparous related: nulliparous, nulligravid, never pregnant, never delivered

Young women related: young women, adolescent, aged under, teenage

Types of study to be included

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved copper intrauterine devices available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over, or that involved copper intrauterine devices not available, or not of the same design and size to those available, in the UK.

Condition or domain being studied

Copper intrauterine contraception in nulliparous and young women

Participants/population

Women who are nulliparous and aged under 30

Intervention(s), exposure(s)

Copper intrauterine devices available or comparable to those in the UK

Comparator(s)/control

Any IUD, other contraceptive or no contraception where applicable

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Context
Copper intrauterine devices (IUDs) are of various shapes, sizes, copper surface area and copper distribution on the frame of the device. There are many types of IUDs available in the UK but none shown to be associated with better outcomes in nulliparous and young women. The identification and use of those IUDs associated with less discontinuation could improve outcomes including satisfaction and continuation rates of intrauterine contraception in nulliparous and younger women.

Main outcome(s)
Copper intrauterine contraception discontinuation rates in nulliparous and young women based on type of IUD

Timing and effect measures

Additional outcome(s)
Reasons for IUD discontinuation

Timing and effect measures

Data extraction (selection and coding)
The abstracts of published articles obtained from the literature and websites searches will be reviewed by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. All retrieved full texts of published articles will be reviewed to agree which studies to include in the systematic review, with disagreements resolved by the third author. All retrieved articles to be included in the systematic review will undergo a quality assessment using a risk of bias tool applicable to the type of study.

Main data to be extracted:

type of copper intrauterine device (IUD)

age of women

gravidity/parity of women

place/time of IUD insertion

IUD discontinuation rate(s)

reason(s) for IUD discontinuation

Risk of bias (quality) assessment
All retrieved articles to be included in the systematic review will undergo a quality assessment. One author will complete the inclusion criteria checklist while the second author will review the checklist, with disagreements resolved by the third author/consensus. Retrieved articles with a high risk of bias will be excluded from the systematic review.

Strategy for data synthesis
Data from the included studies will be extracted using a standardised form by one author while the second author will check these. Disagreements will be resolved by a further review of the study with the third author and consensus. One author will enter the extracted data into Review Manager (RevMan®) Software while the second author will again check these for accuracy. It is planned that aggregate data will be used. However, individual data on the intervention and population of interest (IUDs in nulliparous and young women aged under 30) will be extracted where studies have reported on this subgroup their outcomes in conjunction with other population subgroups or study outcomes.
A quantitative synthesis is planned based on the expected homogeneity of the data to be obtained for the main outcome to be studied. This homogeneous data will be combined for meta-analysis. Heterogeneous

data, some of which is expected to be obtained on the additional outcome, will be narratively synthesised.

Analysis of subgroups or subsets
IUDs of same size and design will be grouped and discontinuation rates presented based on IUD type.

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Anticipated or actual start date
28 January 2019

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31 January 2020

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Nil

Conflicts of interest

Language
English

Country
England

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Contraception; Copper; Female; Humans; Intrauterine Devices; Parity; Pregnancy

Date of registration in PROSPERO
07 February 2019

Date of publication of this version
07 February 2019

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

PROSPERO
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Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

07 February 2019

Table – Search Strategies

Databases and additional sources search	Search term(s) used	Limits	Records identified
Allied and Complementary Medicine (AMED) British Nursing Index (BNI) Cumulative Index to Nursing and Allied Health Literature (CINAHL) Excerpta Medica Database (EMBASE) Nursing and Allied Health Professionals Database (EMCARE) Health Management Information Consortium (HMIC) General Medical Database (MEDLINE) Psychology and Allied Fields (PsychINFO) PubMed	(copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab	Title, Abstract English language	**725**
The Cochrane Library Database of Abstracts and Reviews of Effects (DARE) Turning Research into Practice (TRIP) Bandolier National Electronic Library of Health Medicines and Healthcare products Regulatory Agency (MHRA) Faculty of Sexual and Reproductive Healthcare (FSRH) Royal College of Obstetricians and Gynaecologists (RCOG) Department of Health National Institute for Health and Care Excellence (NICE) Scottish Intercollegiate Guidelines, World Health Organisation (WHO)	'copper intrauterine'	-	**22**
Google Scholar	'copper intrauterine device young nulliparous'	-	

TCu 380A continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(81.60% (95% CI 76.52-86.21%))**
Excluding Abraham et al. (<20)	82.04% (95% CI 76.48-87.04%)
Excluding Abraham et al. (20-25)	78.01% (95% CI 66.60-87.74%)
Excluding Hall and Kutler (18-30)	81.83% (95% CI 76.66-86.49%)
Subgroup 2 (Nulliparous women of any age)	**(80.97% (95% CI 76.04-85.48%))**
Excluding Abraham et al. (>25)	81.99% (95% CI 79.19-84.63%)
Excluding Akintomide et al. (15-37)	81.94% (95% CI 79.41-84.34%)
Excluding Roy et al. (14-33)	80.12% (95% CI 73.92-85.70%)
Overall effect size (all studies)	**(81.93% (95% CI 79.66-84.09%))**
Excluding Abraham et al. (<20)	81.84% (95% CI 79.13-84.40%)
Excluding Abraham et al. (20-25)	81.44% (95% CI 78.16-84.53%)
Excluding Hall and Kutler (18-30)	81.87% (95% CI 79.60-84.03%)
Excluding Abraham et al. (>25)	81.57% (95% CI 78.38-84.58%)
Excluding Akintomide et al. (15-37)	82.14% (95% CI 79.87-84.31%)
Excluding Roy et al. (14-33)	80.92% (95% CI 76.93-84.64%)

TCu 200 continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(73.03% (95% CI 67.63-78.10%))**
Excluding Lewit (15-19)	75.26% (95% CI 73.90-76.59%)
Excluding Lewit (20-24)	73.33% (95% CI 71.62-75.00%)
Excluding Lewit (25-29)	71.78% (95% CI 70.30-73.24%)
Subgroup 2 (Nulliparous women of any age)	**(76.51% (95% CI 72.67-80.14%))**
Excluding Roy et al. (14-33)	76.83% (95% CI 72.49-80.91%)
Excluding Luukkainen et al. (19-35)	76.53% (95% CI 71.86-80.91%)
Excluding Larsen et al. (15-44)	76.85% (95% CI 72.79-80.67%)
Excluding Ostergard and Gunning (18-34)	76.84% (95% CI 72.76-80.69%)
Excluding Lewit (30-34)	75.59% (95% CI 71.42-79.54%)
Excluding Lewit (35-49)	75.20% (95% CI 71.98-78.29%)
Excluding Liedholm and Sioberg (14-40)	77.32% (95% CI 73.40-81.01%)
Excluding Mishell et al. (14-33)	76.84% (95% CI 72.51-80.91%)
Overall effect size (all studies)	**(75.44% (95% CI 72.32-78.43%))**
Excluding Lewit (15-19)	76.43% (95% CI 73.71-79.04%)
Excluding Lewit (20-24)	75.59% (95% CI 71.81-79.17%)
Excluding Lewit (25-29)	76.16% (95% CI 71-60-78.56%)
Excluding Roy et al. (14-33)	75.56% (95% CI 72.16-78.81%)
Excluding Luukkainen et al. (19-35)	75.38% (95% CI 71.89-78.72%)
Excluding Larsen et al. (15-44)	75.60% (95% CI 72.34-78.70%)
Excluding Ostergard and Gunning (18-34)	75.59% (95% CI 72.33-78.71%)
Excluding Lewit (30-34)	74.72% (95% CI 71.59-77.73%)

Excluding Lewit (35-49)	74.37% (95% CI 71.53-77.10%)
Excluding Liedholm and Sioberg (14-40)	75.87% (95% CI 72.61-78.98%)
Excluding Mishell et al. (14-33)	75.56% (95% CI 72.16-78.81%)

TCu 200 discontinuation at 12 months due to pain/bleeding – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(7.05% (95% CI 5.59-8.65%))**
Excluding Lewit (15-19)	7.31% (95% CI 6.52-8.14%)
Excluding Lewit (20-24)	6.31% (95% CI 5.41-7.27%)
Excluding Lewit (25-29)	7.88% (95% CI 7.02-8.78%)
Subgroup 2 (Nulliparous women of any age)	**(12.77% (95% CI 8.48-17.78%))**
Excluding Roy et al. (14-33)	13.10% (95% CI 8.10-19.06%)
Excluding Luukkainen et al. (19-35)	11.02% (95% CI 8.41-13.92%)
Excluding Larsen et al. (15-44)	12.40% (95% CI 7.87-17.76%)
Excluding Ostergard and Gunning (18-34)	12.86% (95% CI 8.20-18.35%)
Excluding Lewit (30-34)	13.61% (95% CI 8.83-19.22%)
Excluding Lewit (35-49)	13.79% (95% CI 9.10-19.25%)
Excluding Liedholm and Sioberg (14-40)	12.08% (95% CI 7.56-17.45%)
Excluding Mishell et al. (14-33)	13.13% (95% CI 8.13-19.08%)
Overall effect size (all studies)	**(10.87% (95% CI 7.98-14.15%))**
Excluding Lewit (15-19)	11.37% (95% CI 8.08-15.12%)
Excluding Lewit (20-24)	11.23% (95% CI 7.70-15.32%)
Excluding Lewit (25-29)	11.52% (95% CI 8.34-15.14%)
Excluding Roy et al. (14-33)	10.90% (95% CI 7.77-14.47%)
Excluding Luukkainen et al. (19-35)	9.32% (95% CI 7.62-11.17%)
Excluding Larsen et al. (15-44)	10.51% (95% CI 7.58-13.86%)
Excluding Ostergard and Gunning (18-34)	10.78% (95% CI 7.77-14.20%)
Excluding Lewit (30-34)	11.23% (95% CI 8.01-14.92%)
Excluding Lewit (35-49)	11.34% (95% CI 8.17-14.94%)
Excluding Liedholm and Sioberg (14-40)	10.26% (95% CI 7.40-13.53%)
Excluding Mishell et al. (14-33)	10.92% (95% CI 7.78-14.50%)

TCu 200 discontinuation at 12 months due to expulsion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(10.52% (95% CI 7.17-14.41%))**
Excluding Lewit (15-19)	8.59% (95% CI 7.74-9.48%)
Excluding Lewit (20-24)	11.21% (95% CI 10.03-12.44%)
Excluding Lewit (25-29)	10.36% (95% CI 9.38-11.38%)
Subgroup 2 (Nulliparous women of any age)	**(4.93% (95% CI 2.93-7.39%))**
Excluding Roy et al. (14-33)	4.85% (95% CI 2.57-7.78%)
Excluding Luukkainen et al. (19-35)	4.17% (95% CI 2.68-5.96%)
Excluding Larsen et al. (15-44)	4.92% (95% CI 2.79-7.58%)
Excluding Ostergard and Gunning (18-34)	4.80% (95% CI 2.69-7.46%)
Excluding Lewit (30-34)	4.74% (95% CI 2.41-7.76%)
Excluding Lewit (35-49)	5.24% (95% CI 3.03-7.99%)
Excluding Liedholm and Sioberg (14-40)	5.84% (95% CI 3.95-8.07%)

Excluding Mishell et al. (14-33)	4.85% (95% CI 2.57-7.77%)
Overall effect size (all studies)	**(6.44% (95% CI 4.49-8.69%))**
Excluding Lewit (15-19)	5.76% (95% CI 4.14-7.61%)
Excluding Lewit (20-24)	6.16% (95% CI 3.87-8.93%)
Excluding Lewit (25-29)	6.16% (95% CI 3.96-8.79%)
Excluding Roy et al. (14-33)	6.55% (95% CI 4.47-8.99%)
Excluding Luukkainen et al. (19-35)	6.01% (95% CI 3.98-8.42%)
Excluding Larsen et al. (15-44)	6.54% (95% CI 4.51-8.91%)
Excluding Ostergard and Gunning (18-34)	6.46% (95% CI 4.43-8.83%)
Excluding Lewit (30-34)	6.47% (95% CI 4.36-8.95%)
Excluding Lewit (35-49)	6.87% (95% CI 4.87-9.18%)
Excluding Liedholm and Sioberg (14-40)	7.29% (95% CI 5.39-9.45%)
Excluding Mishell et al. (14-33)	6.55% (95% CI 4.47-8.99%)

TCu 200 discontinuation at 12 months due to pregnancy – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(2.19% (95% CI 1.47-3.05%))**
Excluding Lewit (15-19)	2.27% (95% CI 1.82-2.75%)
Excluding Lewit (20-24)	1.83% (95% CI 1.35-2.39%)
Excluding Lewit (25-29)	2.63% (95% CI 2.13-3.18%)
Subgroup 2 (Nulliparous women of any age)	**(1.15% (95% CI 0.54-1.95%))**
Excluding Roy et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Excluding Luukkainen et al. (19-35)	0.96% (95% CI 0.38-1.75%)
Excluding Larsen et al. (15-44)	1.18% (95% CI 0.53-2.05%)
Excluding Ostergard and Gunning (18-34)	1.31% (95% CI 0.65-2.16%)
Excluding Lewit (30-34)	1.35% (95% CI 0.70-2.18%)
Excluding Lewit (35-49)	1.31% (95% CI 0.62-2.20%)
Excluding Liedholm and Sioberg (14-40)	1.00% (95% CI 0.42-1.78%)
Excluding Mishell et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Overall effect size (all studies)	**(1.49% (95% CI 0.96-2.13%))**
Excluding Lewit (15-19)	1.39% (95% CI 0.81-2.09%)
Excluding Lewit (20-24)	1.34% (95% CI 0.83-1.94%)
Excluding Lewit (25-29)	1.48% (95% CI 0.87-2.22%)
Excluding Roy et al. (14-33)	1.46% (95% CI 0.89-2.16%)
Excluding Luukkainen et al. (19-35)	1.40% (95% CI 0.83-2.09%)
Excluding Larsen et al. (15-44)	1.53% (95% CI 0.98-2.19%)
Excluding Ostergard and Gunning (18-34)	1.62% (95% CI 1.07-2.26%)
Excluding Lewit (30-34)	1.69% (95% CI 1.18-2.29%)
Excluding Lewit (35-49)	1.64% (95% CI 1.10-2.28%)
Excluding Liedholm and Sioberg (14-40)	1.41% (95% CI 0.88-2.06%)
Excluding Mishell et al. (14-33)	1.46% (95% CI 0.89-2.16%)

Table – Characteristics of studies excluded following full text assessment

Study / Authors	Year	Country	Study Design	Study Objectives	Reasons for Exclusion
Akintomide et al[5]	2021	Austria, Finland, Germany, Poland, Sweden, UK	Prospective cohort	Secondary analysis of continuation, unwanted effects and cost consequences at 1 year in IUD users ≤30 in the European Active Surveillance Study for Intrauterine Devices	Undifferentiable results - IUD type categories based on IUD characteristics rather than brand or name of IUD
Garbers et al[20]	2013	USA	Retrospective records review	Prevalence and predictors of IUD discontinuation at 6 months in 306 Cu T380A users	Undifferentiable results; varied duration; 23 excluded from continuation analysis
Goldstuck[21]	1980	UK	Prospective cohort (selected)	Clinical evaluation of the combined multiload copper 250-mini IUD in selected nulliparous women	Undifferentiable results; disparity between data in tables and text
Hindle[27]	1978	Unable to confirm		Clinical evaluation and follow-up on 3,829 IUD procedures	Full text unobtainable
Lete et al[22]	1998	Spain	Prospective cross-sectional	Evaluation of IUD use in nulliparous women compared to parous women over a 12-year period	Data reported as incidence of events rather than rates
Ogedengbe et al[23]	1991	Nigeria	Prospective cohort	A comparison efficacy and discontinuation at 1 year of multiload and copper-T IUDs sequentially assigned to users	Parity of participants not detailed (mean parity 4); only one nulliparous participant
Patnaik[28]	2003	India	Unable to confirm	Uptake, satisfaction, retention and reasons for discontinuation of the copper T IUD	Full text unobtainable
Petersen et al[29]	1991	Unable to confirm	RCT – double blind	Significance of endometrial cavity length in the clinical performance of IUDs in nulligravidae	Full text unobtainable
Phillips et al[24]	2017	USA	Retrospective records review	Comparison of continuation and performance of levonorgestrel and copper intrauterine devices over 5 years	Undifferentiable results
Sivin and Tatum[25]	1981	USA	Prospective cohort	Clinical performance of the TCu 380A IUD over 4 years	Undifferentiable results
Teal et al[26]	2015	USA	Retrospective records review	Evaluation of the success and safety of intrauterine device (IUD) placement in adolescents based on age and parity	Undifferentiable results

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Table – Quality Assessment of Included Studies Using the Mixed Methods Appraisal Tool (MMAT) version 2018

Study / Authors	*Design Category*	*Responses to MMAT Questions (and Scores: Yes (1) / No (0) / Can't Tell (0)*							
		Screening 1	**Screening 2**	**Appraisal 1**	**Appraisal 2**	**Appraisal 3**	**Appraisal 4**	**Appraisal 5**	**Total**
Abraham et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Akintomide et al 2019	Quantitative, non-randomised	yes	yes	yes	yes	no	yes	yes	6
Allonen et al 1980	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Elkhateeb et al 2020	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Fugere 1990	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Hall and Kutler 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Kaislasuo et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Larsen et al 1981	Quantitative, randomised	yes	yes	can't tell	yes	yes	no	yes	5
Lewit 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Liedholm and Sjoberg 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Luukkainen et al 1979	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Luukkainen et al 1987	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Mishell et al 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Nygren et al 1981	Quantitative, randomised	yes	yes	yes	yes	yes	yes	yes	7
Ostergard and Gunning 1979	Quantitative, randomised	yes	yes	yes	can't tell	yes	no	yes	5
Otero-Flores et al 2003	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Roy et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Sivin and Stern 1979	Quantitative, randomised	yes	yes	can't tell	can't tell	yes	yes	yes	5
Timonen et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7

Tau² Values for Heterogeneity of Included Studies

IUD type	Tau² Values for Heterogeneity of Included Studies for Continuation Rates		
	Nulliparous women aged <30	**Nulliparous women of any age**	**Overall effect size (all studies)**
TCu 380A excluding Otero- Flores data	0.0[a] [19, 34]	0.005 [19, 30, 45]	0.0 [19, 30, 34, 45]
TCu 380A including Otero- Flores data	0.487 [19, 34, 44]	0.005 [19, 30, 44, 45]	0.299 [19, 30, 34, 44, 45]
Smaller TCu 380A[b]	not applicable – only one study group	0.0 [30, 44]	0.0 [30, 44]
TCu 300	not applicable – no study	0.0 [45, 47]	0.0 [45, 47]
TCu 200	0.010 [37]	0.012 [37-39, 41, 43, 45]	0.012 [37-39, 41, 43, 45]
Nova T200	not applicable – no study	0.0 [39, 40]	0.0 [39, 40]
	Tau² Values for Heterogeneity of Included Studies for Discontinuation Rates		
TCu 200 discontinuation due to bleeding/pain	0.001 [37]	0.036 [36-39, 41, 43, 45]	0.025 [36-39, 41, 43, 45]
TCu 200 discontinuation due to expulsion	0.010 [37]	0.018 [36-39, 41, 43, 45]	0.018 [36-39, 41, 43, 45]
TCu 200 discontinuation due to pregnancy	0.002 [37]	0.005 [36-39, 41, 43, 45]	0.004 [36-39, 41, 43, 45]

a – includes women aged 30 from Hall and Kutler study data; b – TCu 380A Nul/Mini TT380 Slimline IUDs

Supplementary material – Doi plots

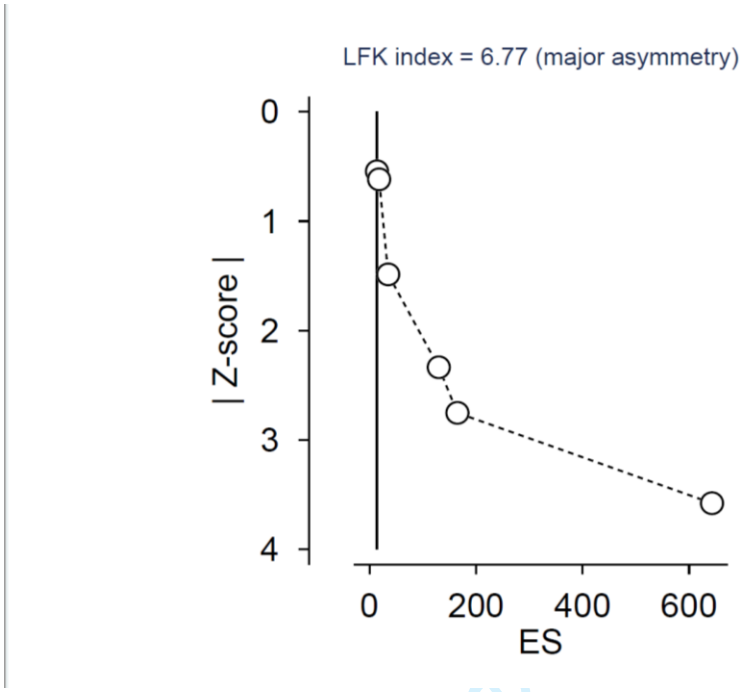

Figure 1 - Doi plot for TCu 380A continuation at 12 months

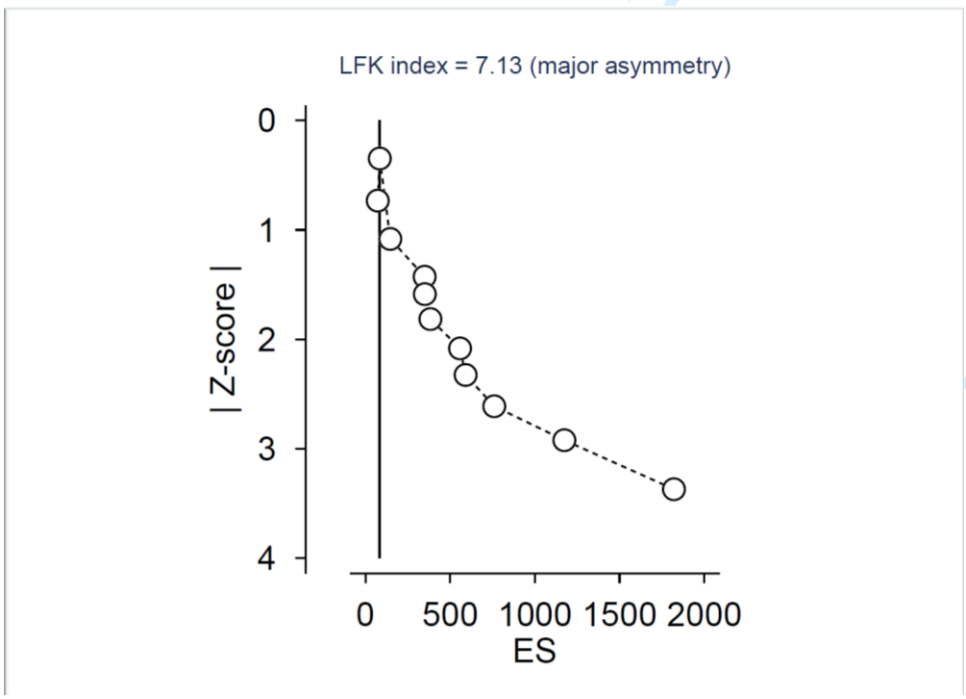

Figure 2 – Doi plot for TCu 200 continuation at 12 months

Supplementary material – Doi plots

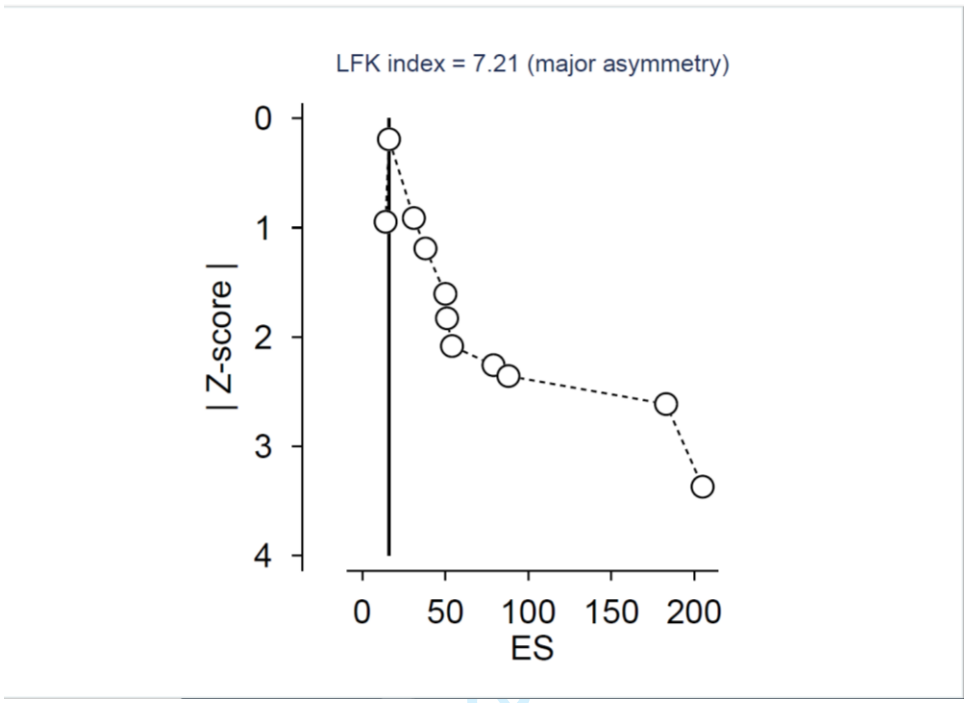

Figure 3 – Doi plot for TCu 200 discontinuation at 12 months due to bleeding/pain

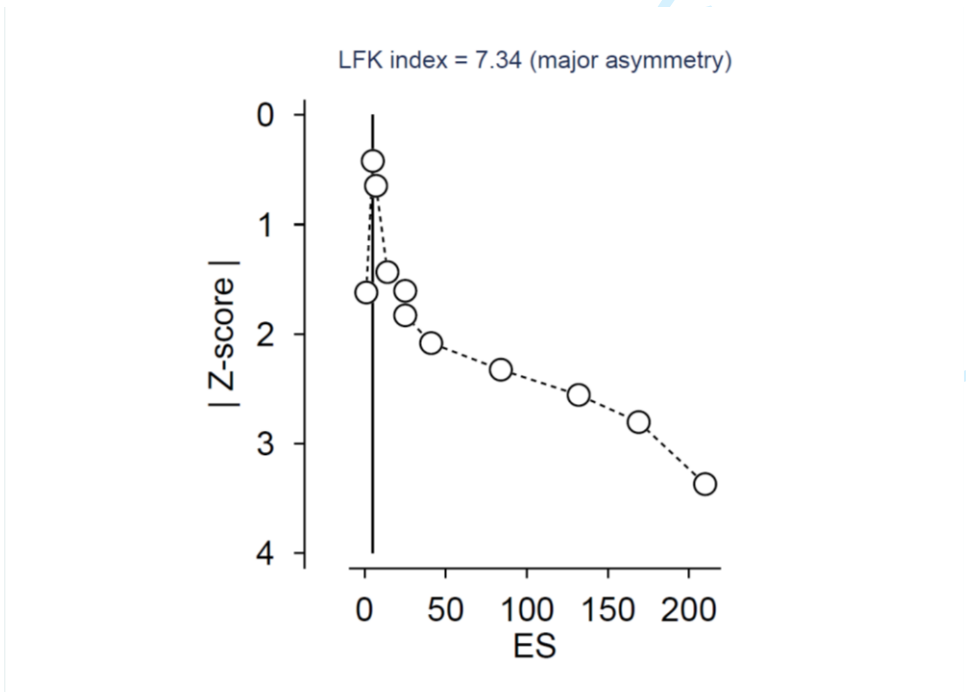

Figure 4 – Doi plot for TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – Doi plots

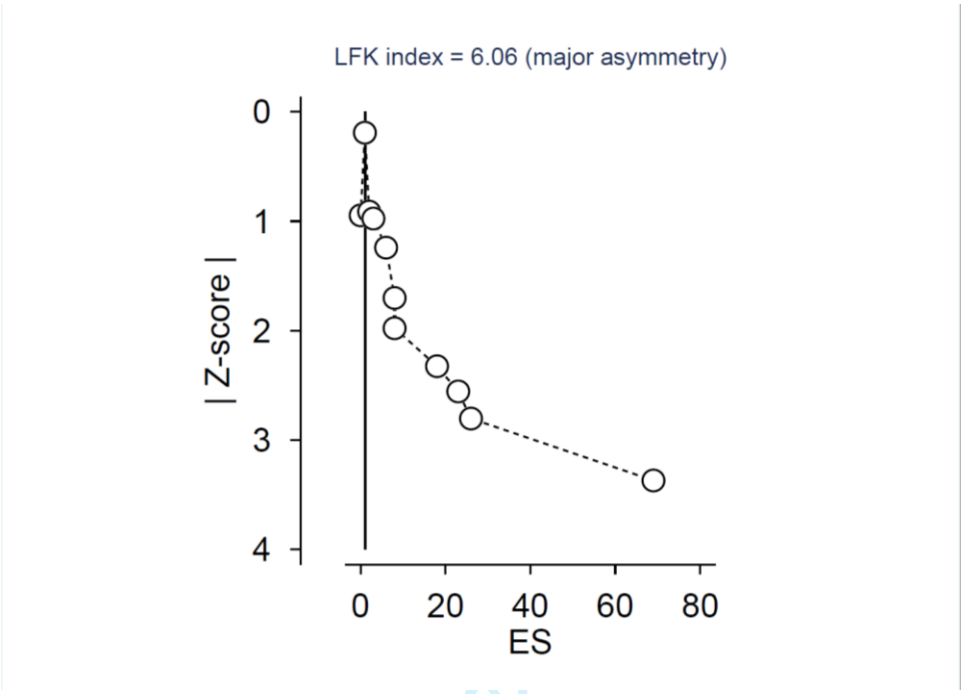

Figure 5 – Doi plot for TCu 200 discontinuation due to pregnancy

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

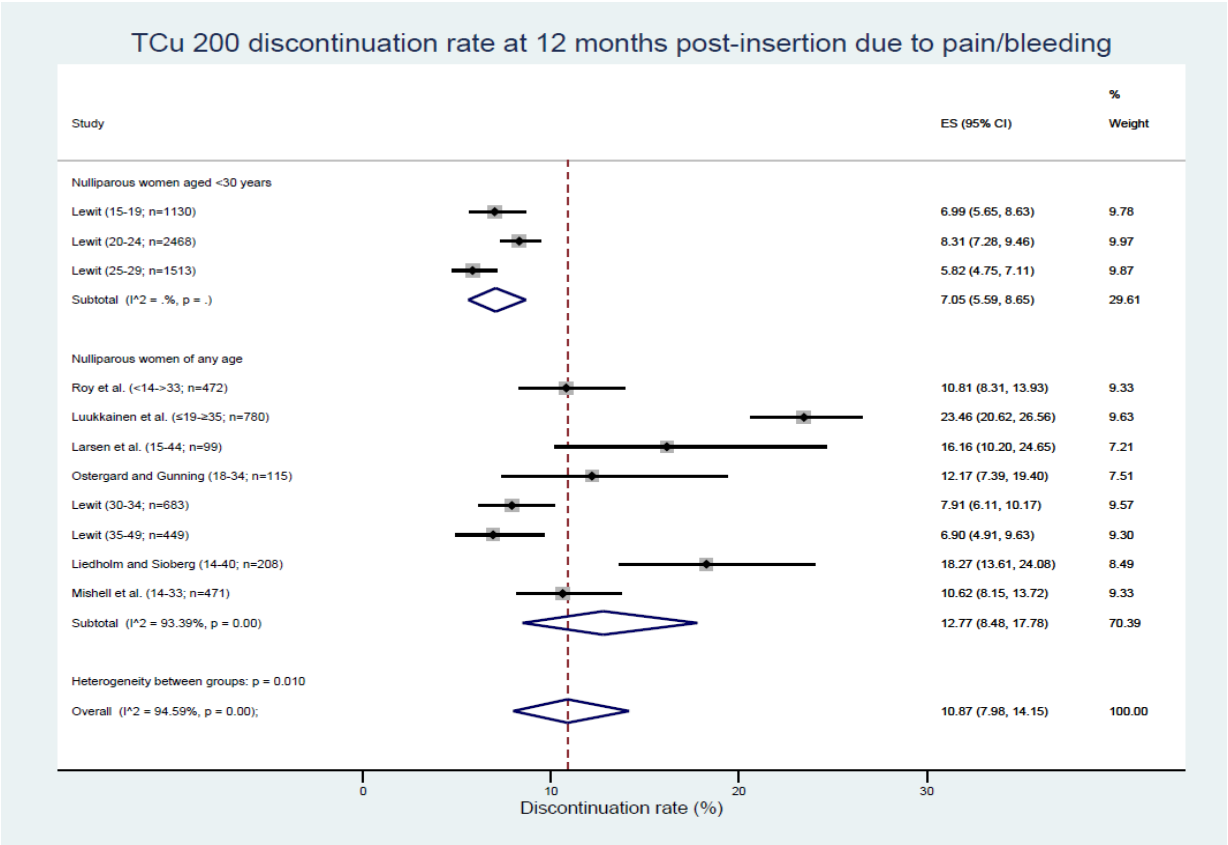

Figure 1 - TCu 200 discontinuation at 12 months due to pain/bleeding

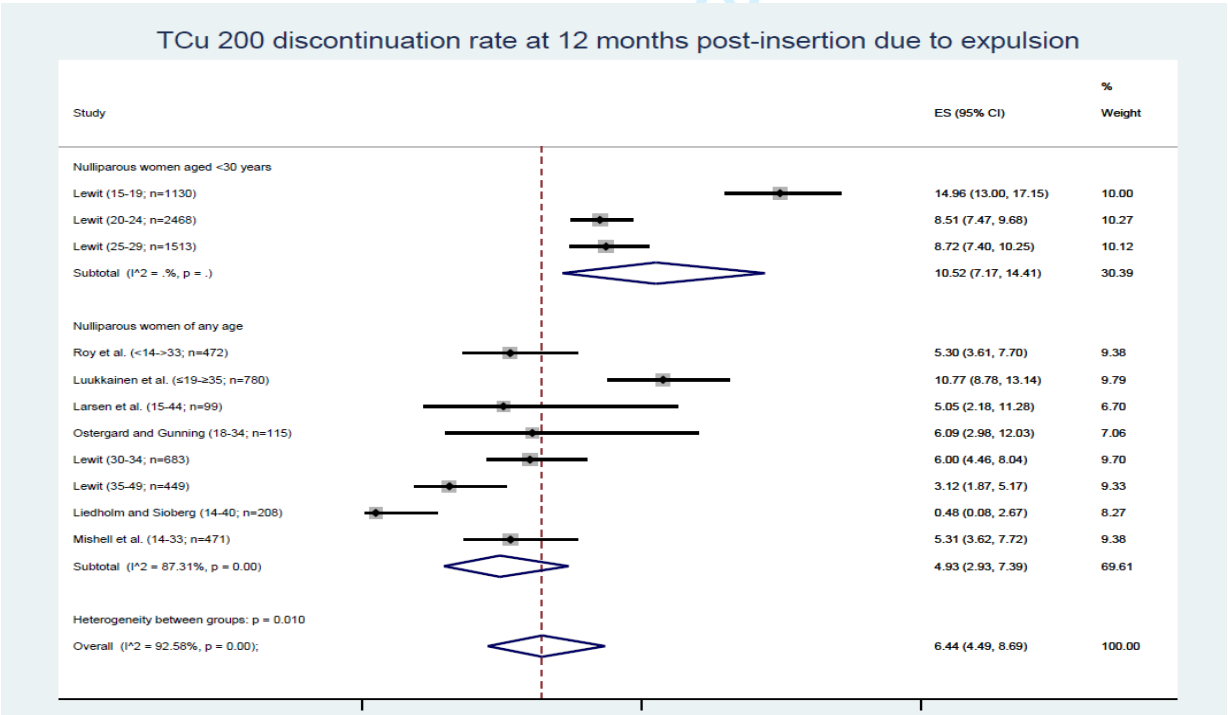

Figure 2 – TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

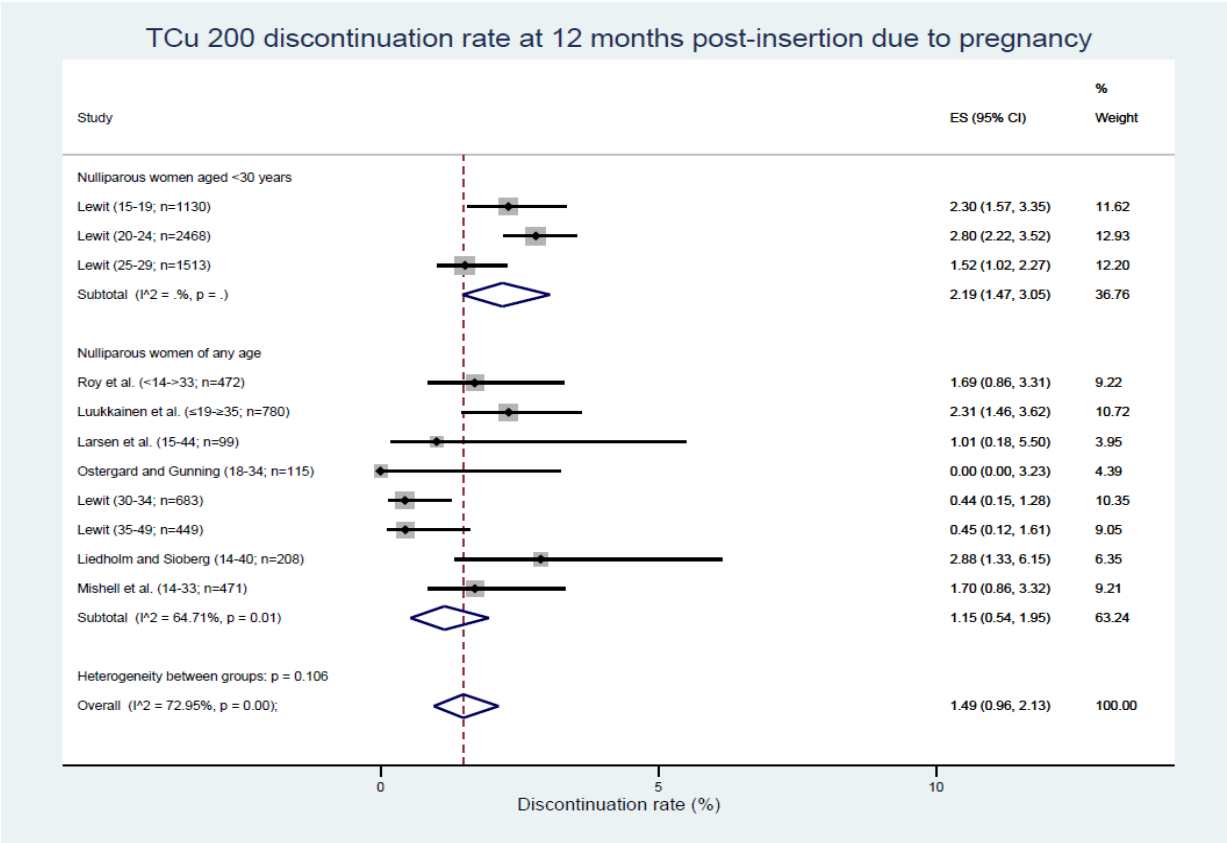

Figure 3 – TCu 200 discontinuation at 12 months due to pregnancy

BMJ Open

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on intrauterine device type

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Keywords:	REPRODUCTIVE MEDICINE, Community gynaecology < GYNAECOLOGY, PUBLIC HEALTH

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TITLE PAGE

A systematic review of copper intrauterine contraception continuation in young nulliparous women based on intrauterine device type

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ABSTRACT

Objectives

No copper intrauterine device (IUD) type is known to better suit young nulliparous women who tend to experience higher rates of IUD discontinuation compared to their older parous counterparts. A systematic review to determine which IUDs have higher continuation rates in young nulliparous women was undertaken.

Design

Systematic review and meta-analyses of available evidence based on IUD type.

Data sources

AMED, BNI, CINAHL, DARE, EMBASE, EMCARE, HMIC, MEDLINE, PsychINFO, PubMed, TRIP, the Cochrane Library electronic databases were searched from inception to 11 May 2022; as well as the Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar websites.

Eligibility criteria

All studies on IUDs currently available in the UK or comparable (same design and size) to those available in the UK, involving nulliparous women of any age including those aged under 30.

Data extraction and synthesis

Independently extracted data were assessed as low risk of bias using the Mixed Methods Appraisal Tool. Random effects meta-analyses of proportions were performed where data, including subgroups, were amenable to quantitative synthesis. Heterogeneity was reported using tau^2 and I^2 statistics, and sensitivity analyses were also performed.

Results

Nineteen studies involving 13,045 nulliparous women were included but the heterogeneity of participant ages, parity and IUD types made quantitative synthesis of outcome data in totality inappropriate. The highest continuation rate obtained was 91.02% [95% CI 88.01-93.64%] for the smaller TCu 380A at 12 months post insertion.

Conclusions

Evidence for IUD use in young nulliparous women based on IUD type remains limited. Smaller-sized IUD types appear better suited to this group of IUD users, however, more research is needed.

PROSPERO registration number CRD42019120969.

SHORT TITLE: Review of IUD continuation rates in young nulliparous women

KEY WORDS: IUD, continuation, discontinuation, reasons, young, nulliparous

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The first reported systematic review exploring IUD types in young nulliparous women
- A wide range of data sources, unrestricted to randomised controlled trials, was reviewed – an approach more representative of the real world
- Articles for inclusion were limited to publications in the English language
- Some data were obtained by calculation and measurements of graphs or figures where this data was not numerically specified in reports
- Most studies did not differentiate between nulligravid and nulliparous participants

REPORTING STATEMENT CHECKLIST

See supplementary material 1

MAIN TEXT: (4234 words)

INTRODUCTION

The highest rates of unintended pregnancy and terminations of pregnancy, which contribute to poor sexual health, are in women aged 20-24 followed by those aged 25-29.[1] Increasing uptake of long-acting reversible contraceptives (LARC), such as copper intrauterine contraception, in these women is yet to yield a proportional reduction in pregnancy terminations. This is attributable to their higher LARC discontinuation rates.[2]

Copper intrauterine contraception is the LARC with the greatest number of brands, with 21 copper intrauterine devices (IUDs) available in the UK.[3] IUDs are of various shapes, sizes, total copper surface area and copper distribution on the IUD frame. They have changed little over the last 40 years. No IUD type has been shown to be associated with better outcomes regarding unwanted effects that lead to early IUD discontinuation. This early IUD discontinuation excludes discontinuation due to IUD user choice alone or the wish to conceive. IUD continuation rates tend to be surrogate for IUD satisfaction and/or acceptability. Studies have shown IUD discontinuation rates to be higher in adolescents and women in their 20s compared to their older counterparts, as well as in nulliparous compared to parous women.[4-8]

Previous systematic reviews and guidance suggest that IUD size and shape may be a factor in discontinuation, and have recommended future research investigate which IUD types are associated with less pain, bleeding and discontinuation.[7, 9-11] The identification and use of IUDs with higher continuation rates and fewer unwanted effects could improve outcomes including IUD satisfaction for young nulliparous women. A systematic review and meta-analysis were therefore undertaken to investigate continuation rates and reasons for discontinuation of IUDs, currently available, or comparable to those currently in use in the UK, based on IUD type involving women aged under 30.

OBJECTIVES

To determine which currently available IUDs have higher continuation rates, in nulliparous women aged under 30, by systematically reviewing published studies. Discontinuation rates and reasons for discontinuation were secondary outcomes.

METHODS

An appraisal of previous systematic reviews, including publications by the Cochrane Collaboration Fertility Regulation Group, Faculty of Sexual and Reproductive Healthcare (FSRH) and National Institute for Health and Care Excellence (NICE) was performed. A search strategy was developed in conjunction with an Electronic Services Librarian. These informed the design of this systematic review and its protocol.

This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline (see supplementary material 1). Its protocol was registered on the International Prospective Register of Systematic Reviews database (PROSPERO; CRD42019120969, see supplementary material 2).[12] The protocol included other studies besides randomised controlled trials (RCTs) reporting on IUD continuation, in case the RCTs determined eligible for inclusion in the systematic review were too few to address the review question.

Selection criteria

Inclusion criteria: Articles published in English, on studies in women who are nulliparous and aged under 30, that involved IUDs available or of the same design and size, to those available in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over 30, that involved IUDs not available, or not of the same design and size to those available in the UK.

Where studies on IUDs currently available in the UK were lacking, studies with IUDs comparable in shape, size, total copper surface area or distribution on the IUD frame to those currently available in the UK were included. Where studies involving only nulliparous women aged under 30 were lacking, studies with nulliparous women of all ages (incorporating those aged under 30), were also included in the review.

Search Strategy

Nine electronic databases - the Allied and Complementary Medicine (AMED), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), Nursing and Allied Health Professionals Database (EMCARE), Health Management Information Consortium (HMIC), General Medical Database (MEDLINE), Psychology and Allied Fields (PsychINFO), and PubMed were searched. The search terms were: (copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab from database inception to 7 February 2021 (updated to 11 May 2022). The following additional sources were searched using the term 'copper intrauterine': the Cochrane Library, Database of Abstracts and Reviews of Effects (DARE), Turning Research into Practice (TRIP) database, National Electronic Library of Health (merged with MEDLINE), Bandolier, Medicines and Healthcare products Regulatory Agency, FSRH, Royal College of Obstetricians and Gynaecologists, Department of Health, NICE, Scottish Intercollegiate Guidelines, and World Health Organisation websites. A Google Scholar search was also undertaken using the term 'copper intrauterine device young nulliparous'. The full search strategy is provided as a supplementary file (supplementary material 3).

Relevant articles published in English were identified by two authors and these were exported into an Endnote library upon completion of all the searches. Following de-duplication, the relevant articles obtained from the searches were exported to Rayyan, a web app for systematic reviews (rayyan.ai). In Rayyan, further de-duplication yielded unique entries of which abstracts, and then full texts, were screened independently by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. Additional citation screening of reference lists of both included and excluded studies was performed. Screening was initially done in batches of 20, then later increased to 50. Agreements were obtained between the first two authors and did not require a third review. Selected articles were RCTs and observational studies published in English, involving IUDs available or comparable to those in the UK, and involving nulliparous women aged under 30.

Quality Assessment and Data Summary

All articles selected for inclusion in the systematic review underwent a quality assessment using the Mixed Methods Appraisal Tool (MMAT), version 2018.[13] The MMAT risk of bias tool was chosen because it was applicable to all the study types selected for inclusion. The highest total MMAT score conforming with best quality was seven, while the lowest possible score equating with poorest quality was zero. Included articles were initially quality assessed by the two authors separately and then agreement was reached.

Data extracted from articles included IUD type, study location(s) and year of publication, age of women, gravidity/parity of women, IUD continuation and discontinuation rates, and reasons for IUD discontinuation. Where a rate was not specified but could be reliably calculated, this was done to one decimal place. If a continuation rate was not specified, this was obtained by subtracting the discontinuation rate from 100, or adding all stated rates for reasons for discontinuation (where these were mutually exclusive) and subtracting from 100, if the report suggested such a calculation to be valid. If a discontinuation rate was not specified, this was obtained by subtracting

a stated continuation rate from 100, or by adding all stated rates for reasons for discontinuation (where these were mutually exclusive), if the report suggested such a calculation was valid. Gross rates (obtained after excluding participants lost to follow up or removals to conceive) were used, except where only net cumulative rates were reported. Measurements were performed to obtain data from published graphs or figures where rates had been reported in this format but not numerically specified.

An Excel data collection form was developed, piloted with three articles selected for inclusion by one author, then revised and amended by the second author before proceeding to data extraction. Data from the 19 selected articles included in the review were extracted by one author into the Excel spreadsheet and checked by the second author.

Data Analysis

Where available data were amenable to quantitative synthesis, random effects meta-analyses of proportions were performed using the metaprop suite of commands on STATA 16. Variances were stabilised using the Freeman-Tukey double arcsine transformation. This approach provides better approximation and leads to results between 0% and 100% when synthesising proportions from small samples and multiple studies in meta-analyses.[14] Where possible, subgroup analysis was performed to examine differences between nulliparous women aged ≤30 years and nulliparous women of any age. Statistical heterogeneity was reported using I^2 and tau^2 statistics, since random effects meta-analyses was being performed. The I^2 value describes the percentage of the variability in effect estimates that is due to statistical heterogeneity (reflecting methodological diversity among the included studies) as opposed to chance. Conventionally, while an I^2 value <40% may not be significant, a value >50% may represent substantial heterogeneity and a value >75% may indicate considerable heterogeneity.[15] The tau^2 statistic measure of 'between-study variance', unlike the I^2 statistic, is not affected by size of included studies in a meta-analysis and hence may be considered more appropriate for estimating heterogeneity.[16] The effect of removing individual studies on the overall effect size (ES) was explored in sensitivity analyses (supplementary material 4). Publication bias was examined by producing Doi plots and generating LFK index values, being considered a more appropriate measure of publication bias than funnel plots/Egger's test when performing meta-analyses of proportions.[17]

Patient and Public Involvement

The FSRH is the UK organisation committed to meeting the highest SRH standards, ensuring improvements in population SRH and supporting SRH professionals. The FSRH's Contraceptive Priority Setting Partnership in liaison with the James Lind Alliance yielded over 700 responses from patients, practitioners and the public that identified: 'Which interventions increase uptake and continuation of effective contraception including long-acting methods…?' as the top SRH research priority.[18] This influenced the research aims. IUD users attending a sexual health clinic over a four-week period were consulted about improving access to and use of intrauterine contraception. Their suggestions, which included studying women's experiences with IUDs, were used in developing the research question, aim, and study design. The Consumer Panel of the North East

Research Design Service was also consulted and the proposed research presented to them. The research plan was modified in line with their feedback.

RESULTS

Only one study, a prospective (non-RCT) cohort study, provided information on an IUD available in the UK, solely involving nulliparous users aged under 30.[19] This was inadequate to address the review question. As per the systematic review protocol, other studies on IUDs currently available in the UK or IUDs comparable to those available in the UK (Box 1) involving nulliparous women of all ages (so not limited to those aged under 30) were also screened. An IUD was considered comparable if at least two out of its four characteristics (copper surface area, shape/design, width and arms flexibility) equated with IUDs currently used in the UK. So, for example, the Nova T200 was comparable because it has the same shape/design as a Nova T380, the same width as a Nova T380/Cu T380A/ TCu 380A and TT380 slimline, and the same flexible arms as a Nova T380 (Box 1).

Box 1 – Characteristics of IUDs in included studies

IUD brand / name	Copper (mm^2)	shape / design	width (mm)	arms' flexibility
Currently available in the UK				
Cu T380A / TCu 380A / TT380 Slimline	380	T with arm bands	>30	No
TCu 380A Nul / Mini TT380 slimline	380	T with arm bands	23.2	No
Multiload Cu 375	375	Ω	16 – 20.5	Yes, flex down
Nova T 380	380	T without arm bands	>30	Yes, flex up
Comparable to those available in the UK				
Nova T 200	200	T without arm bands	≥30	Yes, flex up
TCu 300	300	T without arm bands	>30	No
Cu T200 / TCu 200	200	T without arm bands	>30	No
TCu 220C	220	T without arm bands	>30	No

Thirty records were obtained and their full texts assessed where possible. Eleven records were excluded, either for lack of usable outcome data (n=8; [5, 20-26]) or because their full texts were unobtainable (n=3; [27-29]) (see supplementary material 5). A total of 19 studies on IUDs available or comparable to those available in the UK, involving 13,045 nulliparous women, were included in the systematic review (Table 1).[19, 30-47] Figure 1 depicts a PRISMA flow diagram detailing the search and selection process.[48]

Table 1 – Characteristics of Included Studies

Study / Authors	Year	Country	Study Design	Study Objectives	IUDs in study	Quality (MMAT score)
Abraham et al [19]	2015	USA	Prospective cohort	Relationship among young age, nulliparity, and continuation of long-acting reversible contraceptives	Copper T380A	Good (7)
Akintomide et al [30]	2019	UK	Retrospective records review	Discontinuation rates and reasons for discontinuation at 1 year of the small-sized Mini TT380 Slimline IUD compared with the standard-sized TT380 Slimline	Mini TT380 slimline TT380 slimline	Good (6)
Allonen et al [31]	1980	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 2 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (6)
Elkhateeb et al [32]	2020	Egypt	Prospective cohort	Acceptability of IUD use in nulliparous women by both women and health care providers	Copper T380A	Good (7)
Fugere [33]	1990	Canada	Prospective cohort	Clinical performance of the Nova T200 IUD over 5 years	Nova T200	Good (7)
Hall and Kutler [34]	2016	USA	Prospective cohort	Experience and satisfaction of nulliparous intrauterine contraception users at 1, 6, 12 and 18 months	Copper T380A	Good (7)
Kaislasuo et al [35]	2015	Finland	Prospective cohort	Menstrual characteristics and ultrasonographic uterine cavity measurements predict bleeding and pain in nulligravid women using intrauterine contraception	Nova T380	Good (7)
Larsen et al [36]	1981	Denmark	RCT – patient blind	Comparison of clinical performances of Progestasert and Copper T200 at 12 months	Copper T200	Good (5)
Lewit [37]	1973	USA	Prospective cohort	Two years' experience of the Copper T200	Copper T200	Good (7)
Liedholm and Sjoberg [38]	1974	Sweden	Prospective cohort	Two years' experience with the Copper T200 and comparison between nulliparous and parous women	Copper T200	Good (7)
Luukkainen et al [39]	1979	Denmark, Finland Sweden	RCT – double blind	Experience and clinical performance of the Nova T200 and Copper T200 at 12 months	Nova T200 Copper T200	Good (6)
Luukkainen et al [40]	1987	Denmark, Finland, Hungary, Norway, Sweden	RCT – no blinding	Use-effectiveness and clinical performance of levonorgestrel- and copper-releasing intrauterine devices at 12 months	Nova T200	Good (6)

Mishell et al [41]	1973	USA	Prospective cohort	Continuation and clinical performance of TCu 200 in nulliparous women	Copper T200	Good (7)
Nygren et al [42]	1981	Denmark, Finland Sweden	RCT – double blind	Continuation rates and reasons for discontinuation at 3 years of the Nova T200 and Copper T200	Nova T200 Copper T200	Good (7)
Ostergard and Gunning [43]	1979	USA	RCT – blinding not stated	Continuation and clinical performances of Copper T200 and Dalkon Shield in nulligravid women at 12 months	Copper T200	Good (5)
Otero-Flores et al [44]	2003	Mexico	RCT – single (patient) blind	Comparison of clinical performance of three different IUDs in nulliparous women	Copper T380A Copper T380A Nul Multiload 375 sl	Good (6)
Roy et al [45]	1974	USA	Prospective cohort	Experience with three different IUD models in nulliparous women at 1 year	Copper T380A Copper T300 Copper T200	Good (7)
Sivin and Stern [46]	1979	USA	RCT – double blind	Experience of three different IUDs in nulliparous and parous women	Copper T380A Copper T220C Copper T200	Good (5)
Timonen et al [47]	1974	Finland	Prospective, single (patient) blind	Use-effectiveness of Copper T300 at 1 year	Copper T300	Good (7)

All included studies were generally of good quality (mean 6.42 [5-7]; see supplementary material 6 for quality and risk of bias assessments). The lowest MMAT score of five obtained was awarded to three RCTs published in 1979 and 1981 and may relate to inadequate reporting.[36, 43, 46] Their reports did not confirm that randomisation had been appropriately performed, [36, 46] randomised groups were comparable at baseline, [43, 46] nor that outcome assessors were blinded to the intervention provided. [36, 43]

Although the outcome data obtained were considered homogenous, studies' designs, participant ages and parity, and IUD types were not; making a quantitative synthesis of the outcome data in totality inappropriate. Results were therefore grouped into three to include studies involving: 1. IUD types currently available in the UK and only nulliparous women aged ≤30; 2. IUD types currently available in the UK and nulliparous women of all ages; 3. IUD types comparable to those available in the UK and nulliparous women of all ages (Table 2). The estimated continuation rates at 12 months by IUD type, obtained from the included studies with data amenable to synthesis, is reported in Table 3. Tau^2 values for heterogeneity of the included studies is provided separately (see supplementary material 7).

Table 2 – Summary of Findings

Study	IUD types (N[µ])	Age at insertion (y)	Study period	Continuation rates % (n)[CI]	Discontinuation rates % (n)	Removal for bleeding/pain % (n)	Expulsion % (n)	Pregnancy % (n)
Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30								
RCT								
Otero-Flores et al 2003 [44] [µ §]	TCu 380A (375) TCu 380A Nul (367) ML Cu 375 sl (374)	23.2±6.8 22.4±6.6 22.6±6.4	12 months	30.7 (115) 91.3 (335) 89.0 (333)	69.3 (260) 8.7 (32) 11.0 (41)	61.6 (231) 3.81 (14) 6.68 (25)	3.47 (13) 1.91 (7) 1.87 (7)	1.07 (4) 0.54 (2) 0.00 (0)
Non-RCT								
Abraham et al 2015 [19]	Cu T380A (201) Cu T380A (44) Cu T380A (201) Cu T380A (44)	20 - 25 <20 20 - 25 <20	12 months 24 months	82 [76-87] 79 [64-89] 73 [66-79] 64 [48-77]	ns ns	ns ns	ns ns	ns ns
Hall and Kutler 2016 [34]	Cu T 380A (21)	18 - 30	12 months	73.7 (14)	26.3 (5)	10.5 (2)	10.5 (2)	5.26 (1)
Studies of IUD types currently available in the UK involving nulliparous women of all ages								
RCTs								
Sivin and Stern 1979 [46][¶,a]	TCu 380A (2254) TCu 220C (1301) TCu 200 (4215)	<20 - 35+ <20 - 35+ <20 - 35+	2y	55.7 57.8 54.2	44.3 42.2 45.8	21.9 19.5 16.8	7.8 9.8 9.8	0.8 1.6 5.1
Non-RCTs								
Akintomide et al 2019 [30]	TT380 Slimline (27) Mini TT380 Slimline (53)	15 – 37 16 - 37	1y	66.7 (18) 86.8 (46)	33.3 (9) 13.2 (7)	ns ns	3.7 (1) 3.77 (2)	0 (0) 0 (0)

Elkhateeb et al 2020 [32]	TCu 380A (90)	16 - >30	6 months	94.4 (85)	5.6 (5)	ns	0 (0)	ns
Kaislasuo et al 2015 [35]§	Nova T380 (42)	18 - 43	1y	83.3 (35)	16.7 (7)	ns	4.76 (2)	ns
Roy et al 1974 [45]	TCu 380A (785) TCu 300 (347) TCu 200 (472)	<14 - >33 15 - >33 <14 - >33	12 months	81.9 80.7 74.2	18.1 19.3 25.8	9.1 9.2 10.7	3.8 6.1 5.4	0.2 0.6 1.7
Studies of IUD types comparable to those available in the UK involving nulliparous women of all ages								
RCTs								
Luukkainen et al 1979 [39][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	12 months	ns ns	ns ns	15.3 23.4	6 10.8	0.53 2.3
Allonen et al 1980 [31][a,b]	Nova T200 (ns) Cu T200 (ns)	≤19 - ≥35 ≤19 - ≥35	24 months	ns ns	ns ns	23.5 24	6.5 14	1.14 5.28
Nygren et al 1981 [42][a]	Nova T200 (ns) Cu T200 (ns)	<20 - >35	36 months	36.9 31.0	ns ns	28.3 (74) 28.2 (68)	10.3 (27) 10.7 (26)	1.5 (4) 6.5 (15)
Larsen et al 1981 [36][a]	Cu T200 (99)	15 - 44	12 months	73	27[α]	16	5	1
Luukkainen et al 1987 [40]	Nova T200 (77)	17 – 40	12 months	73.1	26.9[α]	10.4	9.2	0
Ostergard and Gunning 1979 [43]	TCu 200 (117) TCu 200 (115)	18 – 34	6 months 12 months	88.9 (104) 73.0 (84)	11.1 (13) 27.0 (31)	6.0 (7) 12.2 (14)	3.41 (4) 6.09 (7)	0 (0) 0 (0)
Non-RCTs								
Fugere 1990 [33]	Nova T200 (54)	17 - 42	24 months	ns	ns	17.2	1.9	0
Lewit 1973 [37]	TCu-200 (2099) Nulligravid subgroup: TCu-200 (1585)[§] Age subgroups: TCu-200 (1130)	15-49 15-49 15 – 19	1y 1y 1y	73.3 75.9 67.3	26.7 24.1 32.7	9.4 9.6 7	10.7 8.7 15	1.3 0.8 2.3

	TCu-200 (2468) TCu-200 (1513) TCu-200 (683) TCu-200 (449)	20 – 24 25 – 29 30 – 34 35 - 49	1y 1y 1y 1y	73.8 77.6 81.7 85.2	26.2 22.4 18.3 14.8	8.3 5.8 7.9 6.8	8.5 8.7 6 3.1	2.8 1.5 0.4 0.3
Liedholm and Sjoberg 1974 [38]	T-Cu 200 (208) `	14 - 40	12 months 24 months	70.2 60.3	29.8 39.7	18.1 28	0.5 0.5	2.9 (6) 2.9 (6)
Mishell et al 1973 [41][a]	TCu 200 (471)	14-33	3 months 6 months 12 months	92.6 84.5 74.2	7.4 15.5 25.8	2.8 5.8 10.7	2.6 4.7 5.4	0.2 0.4 1.7
Timonen et al 1974 [47]	T Cu-300 (138)	<25 - 40+	12 months	84.7	15.3	7.2	1.6	1.6

RCT – randomised controlled trial; ns – not stated; µ - sample size or participants excluding those lost to follow up or removals to plan pregnancy; § - nulligravid women only; ¶ - a combination of double blind studies; α – not stated; obtained by subtraction of continuation rate from 100; a – net cumulative rates; b – data obtained from graphs or figures

Table 3 – Estimated continuation rates at 12 months of IUD types from included studies

	Continuation rates with numbers of patients (*n*), and statistical heterogeneity (tau² and I²) values [of studies included in subgroup]		
IUD type	**Nulliparous women aged <30**	**Nulliparous women of any age**	**Overall effect size (all studies)**
TCu 380A[a]	81.60% (95% CI 76.52-86.21%)[b] (*n*=264; tau²=0.0; I^2=0.0%, p=0.69) [19, 34]	80.97% (95% CI 76.04-85.48%) (*n*=971; tau²=0.005; I^2=27.6%, p=0.25) [19, 30, 45]	81.93% (95% CI 79.66-84.09%) (*n*=1235; tau²=0.0; I^2=0.0%, p=0.62)[19, 30, 34, 45]
Smaller TCu 380A[c]	not applicable – only one study group	91.02% (95% CI 88.01-93.64%) (*n*=420; tau²=0.0; I^2=0.0%, p=0.51) [30, 44]	91.02% (95% CI 88.01- 93.64%) (*n*=420; tau²=0.0; I^2=0.0%, p=0.51) [30, 44]
TCu 300	not applicable – no study	81.92% (95% CI 78.35-85.24%) (*n*=485; tau²=0.0; I^2=17.3%, p=0.27) [45, 47]	81.92% (95% CI 78.35-85.24%) (*n*=485; tau²=0.0; I^2=17.3%, p=0.27) [45, 47]
TCu 200	73.03% (95% CI 67.63-78.10%) (*n*=5111; tau²=0.010; I^2=94.2%, p=<0.01) [37]	76.51% (95% CI 72.67-80.14%) (*n*=3277; tau²=0.012; I^2=84.0%, p=<0.01) [37-39, 41, 43, 45]	75.44% (95% CI 72.32-78.43%) (*n*=8388; tau²=0.012; I^2=89.9%, p=<0.01) [37-39, 41, 43, 45]
Nova T200	not applicable – no study	73.21% (95% CI 70.10-76.22%) (*n*=818; tau²=0.0; I^2=0.0%, p=0.94) [39, 40]	73.21% (95% CI 70.10-76.22%) (*n*=818; tau²=0.0; I^2=0.0%, p=0.94) [39, 40]

a – excludes Otero-Flores et al study data; b – includes women aged 30 from Hall and Kutler study data; c – TCu 380A Nul/Mini TT380Slimline IUDs

Studies of IUD types currently available in the UK only involving nulliparous women aged ≤30

Three studies - Abraham et al (2015), Hall and Kutler (2016) and Otero-Flores et al (2003) - reported on IUDs in women aged ≤30 involving the Copper T380A IUD (TCu 380A or Cu T380A).[19, 34, 44] The TCu 380A data obtained from Otero-Flores et al (2003) was an outlier, with 30.7% reported as the continuation rate at 12 months. [44] This was much lower than for the other two studies with a pooled estimate of 81.60% (95% CI 76.52-86.21%).[19, 34] (Figure 2) When the Otero-Flores et al data were included in this TCu 380A meta-analysis, nulliparous women ≤30 years of age at 12 months had a continuation rate of 66.98% [95% CI 32.09-93.90%]. (Figure 3)

Continuation was also higher with age at 12 and 24 months when nulliparous TCu 380A IUD users aged <20 and 20 - 25 were compared (Table 2).[19]

Studies of IUD types currently available in the UK involving nulliparous women of all ages

Five studies reporting data pertaining to seven population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the TCu 380A IUD at 12 months post insertion.[19, 30, 34, 44, 45] The pooled estimated continuation rate of the Copper T380A IUD type in nulliparous women of all ages from four studies was 81.93% (95% CI 79.66-84.09%).[19, 30, 34, 45]. Additionally, statistical heterogeneity was found to be low/absent but was not statistically significant ($tau^2 = 0.0$, $I^2 = 0.0\%$, $p = 0.62$). Sensitivity analysis confirmed that the overall effect size was largely robust to the exclusion of individual studies (-1.01% to +0.21% change in effect size; see supplementary material 4).

The estimated TCu 380A continuation rate in nulliparous women of all ages remained good at 71.65% (95% CI 51.15-88.44%; $tau^2 = 0.299$, $I^2 = 98.4\%$, $p = <0.01$) when the Otero-Flores et al data was included.[44] (Figure 3). An LFK index value of 6.77 identified major Doi plot asymmetry consistent with publication bias (see supplementary material 8).

Individual studies showed the TCu 380A had higher discontinuation related to bleeding/pain and expulsion [34, 44, 46] when compared to IUDs of smaller size or those with flexible arms [30, 44](Table 2).

The highest continuation rates at 12 months were reported with smaller-sized IUDs - the Copper 380A Nul (TCu 380A Nul - 91.3%), Multiload Copper 375 sl (ML Cu 375 sl - 89%), and Mini TT380 slimline (86.8%) (Table 2). These data were obtained from only two studies whose participants were aged 15 to 37.[30, 44] Meta-analysis of continuation rate data on the TCu 380A Nul/Mini TT380 slimline IUD type gave a weighted average of 91.02% (95% CI 88.01-93.64%) (Figure 4). These smaller IUDs were also associated with the lowest rates of removals for bleeding/pain (3.80 – 6.68%) and expulsion (1.87 – 3.77%) reported in nulliparous women at 12 months (Table 2).

Studies of IUD types comparable to those in the UK involving nulliparous women of all ages

Two studies reporting data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T300 IUD (TCu 300) at 12 months post insertion, with an overall effect size of 81.9% (95% CI 78.35-85.24%, see figure 5). [45, 47]

Seven studies reporting data pertaining to 11 population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Copper T200 IUD (TCu 200 or Cu T200) at 12 months post insertion, with a weighted average of 75.44% (95% CI 72.32-78.43%, see figure 6).[36-38, 40, 41, 43, 45] These studies were also amenable to meta-analysis examining the proportion of women discontinuing the TCu 200 at 12 months post insertion due to bleeding and/or pain, expulsion and pregnancy (see supplementary material 9). For these meta-analyses, nulliparous women aged <30 years compared to nulliparous women of any age were less likely to continue to use the TCu 200 at 12 months (73.03% [95% CI 67.63-78.10%] versus 76.51% [95% CI

72.67-80.14%]), and less likely to discontinue the TCu 200 due to bleeding and/or pain (7.05% [95% CI 5.59-8.65%] versus 12.77% [95% CI 8.48-17.78%]). Nulliparous women aged <30 years compared to nulliparous women of any age were however more likely to discontinue the TCu 200 due to expulsion (10.52% [95% CI 7.17-14.41%] versus 4.93% [95% CI 2.93-7.39%]) and pregnancy (2.19% [95% CI 1.47-3.05%] versus 1.15% [95% CI 0.54-1.95%]). The overlapping confidence intervals for these two effect sizes suggest the difference in effect is not statistically significant, and therefore may or may not be clinically significant. Statistical heterogeneity values for overall TCu 200 continuation rates as well as discontinuation rates for bleeding/pain and expulsion were - $tau^2 = 0.012$, $I^{\wedge 2} = 89.9\%$, p = <0.01; $tau^2 = 0.025$ $I^{\wedge 2} = 93.2\%$, p = <0.01; and $tau^2 = 0.018$, $I^{\wedge 2} = 96.3\%$, p = <0.01 respectively (see figure 6 and supplementary material 9). Sensitivity analyses confirmed that the overall effect sizes were largely robust due to the exclusion of individual studies (see supplementary material 4). In all cases, their LFK index values identified major Doi plot asymmetry consistent with publication bias (see supplementary material 8).

Continuation rates were seen to progressively improve with age where Lewit (1973) reported rates in nulliparous TCu 200 users by age groups 15 – 19, 20 – 24, 25 – 29, 30 – 34, and 35 – 49.[37] (Table 2)

Two studies reporting data pertaining to two population subgroups were amenable to meta-analysis examining the proportion of women continuing to use the Nova T200 at 12 months post insertion,with a weighted average of 73.21% (95% CI 70.10-76.22%, see figure 7).[39, 40]

Studies also showed that IUDs with flexible arms (Nova T, Multiload) were associated with higher continuation and lower removal rates for bleeding/pain, expulsion and pregnancy when compared to IUDs with rigid arms (Cu T or TCu).[31, 39, 44] (Table 2).

DISCUSSION

Findings and Interpretation

Evidence on IUDs currently used in nulliparous women aged under 30 is limited. These findings estimate the continuation rate for the recommended TCu 380A IUD [11] to be 81% at 12 months post insertion based on four studies involving young nulliparous women.[19, 30, 34, 45] This was the same estimate for the TCu 300 based on two studies.[45, 47] Smaller sized and flexible IUDs had higher continuation rates of 86-91% in this group of women, based on two studies, as well as fewer removals for bleeding/pain and expulsion compared to the TCu 380A or IUDs of the same rigid design or size.[30, 44] Lower continuation rates of 75% and 73% were obtained for the TCu T200 and Nova T200 based on eight studies.[36-41, 43, 45]

The study by Otero-Flores et al was the only reported RCT solely involving IUDs currently used in the UK with nulliparous women aged ≤30.[44] Over a thousand nulliparous women aged 15 to 30 were randomised to receive three different IUDs - TCu 380A (width 32mm), TCu 380A Nul (width 23mm) and ML Cu 375 sl (width ≤20mm), the latter two being primarily designed for nulliparous women. The TCu 380A overall rate of discontinuation (69.3%) and bleeding/pain as a reason for discontinuation (61.6%) were significantly higher than for TCu 380A Nul (8.7% and 3.81%) and ML Cu 375 sl (11.0% and 6.68%), as well as significantly different from rates reported by other included studies involving the TCu 380A.This could be because the TCu 380A considerably differs

in size from the TCu 380A Nul and ML Cu 375 sl IUDs, and Otero-Flores et al also exclusively involved nulligravid participants (as opposed to nulliparous).

Sivin and Stern (1979) was the only other RCT involving a TCu 380A that reported separately on nulliparous users.[46] However, their TCu 380A discontinuation and bleeding/pain rates, 44.3% and 21.9% respectively, were obtained at two years and their participants were aged <20 to 35+ years.

The disparity in discontinuation rates reported by Otero-Flores et al [44] and Sivin and Stern [46]suggests that the findings by Otero-Flores et al may be unreliable. But it may in fact be inappropriate to directly compare other studies' TCu 380A data, including that of Sivin and Stern, to Otero-Flores et al's data. Their studies' designs as well as participants' ages, gravidity/parity, environments and reported durations of use were not the same. Otero-Flores et al's participants were younger (≤30 years), exclusively nulligravid, 'highly educated' and based in a Mexico city with free access to healthcare in the millenial era, with the study being single-(patient) blinded. This contrasts with most studies involving the TCu 380A or similar IUDs where participants were more likely to be aged 30 years or older and parous with unspecified educational attainment. The Sivin and Stern study population were living and accessing healthcare (which was not stated to have been free) across the United States, in the late 1970s (over two decades earlier than the Otero-Flores study, and not long after the Dalkon Shield era), with the study being double-blinded. Other explanations for the disparity could be that the modern younger nulligravid cohort may be less tolerant of unwanted IUD effects, and that some contraceptive research may be less likely to acknowledge participants' reasons and wishes for early IUD discontinuation.[49]

The TCu 200 IUD was ≥33mm in width and/or height so perhaps larger than a standard-sized TCu 380A.[50] IUD size may contribute to pain, which may explain TCu 200's lower continuation rates compared to the TCu 380A. However the TCu 300, of the same design and size as the TCu 200,[47] unexpectedly had a higher continuation rate than the TCu 200. This is because higher copper content has been associated with more bleeding which contributes to early discontinuation.[51] The TCu 300 data were limited to two studies that both had total MMAT scores of 7,[45, 47] whereas the TCu 200 data had been obtained from seven studies with MMAT scores of 7,[37, 38, 41, 45] 6,[39] and 5[43] respectively.

Strengths and Limitations

This is the first systematic review to explore IUD types in younger aged nulliparous women. It has included all observational studies that provided information on IUD continuation or reasons for discontinuation in this user group. Non-restriction to RCTs may be considered a limitation, but a realist approach of expanding the inclusion criteria where RCT evidence is lacking could be commendable and more representative of routine practice. Using the MMAT, the quality of reviewed and included studies in this systematic review was good overall.

Articles for inclusion were unfortunately limited to publications in the English language. There was an absence of studies on IUDs currently available in the UK and solely involving women aged under 30. This warranted including all ages if women under 30 years were involved, and up to (≤) 30 years for the TCu 380A data and meta-analysis because of the ages of the Hall and Kutler study participants (18-30 years). Many studies did not report all the required information, hence some included studies had missing information (Table 2). Most studies did not differentiate between

nulligravid and nulliparous participants, many age ranges were not specific (e.g. ≤19 - ≥35), while some reports e.g. Sivin and Stern (1979) were a combination of individual studies [46]. Similarly, it appeared common for older studies to only state numbers (rather than rates or percentages), or only graphically depict data on continuation rates or unwanted effects. It is also not unusual for a systematic review to include such studies, e.g. Hubacher (2007), and to calculate or measure rates accordingly, as has been done in this review.[7] These are potential limitations which are not considered to impact the validity of the review. All mitigating actions that were taken have also been appropriately stated.

Relevance of Findings

IUD use in young nulliparous women has been established to be safe, effective and acceptable.[52-54] It is recommended that women are provided with the most appropriate IUD types for their uterine cavity size. Uterine cavity width (measurable using a cavimeter or ultrasonography, not routinely practised) in addition to uterine length (routinely measured using a hysterome) should be recognised as influencing IUD type choice.[29, 55-57] This systematic review suggests which IUD types may be more suitable for younger aged nulliparous women and emphasises the need for further research.

Recommendations

Strengthening the evidence for contraceptive choice and continuation is needed to improve sexual health in younger aged women. Prospective observational studies that include various IUD designs and types, and detailed reporting of users' experiences could facilitate a better understanding of early IUD discontinuation and reasons for discontinuation based on IUD types. Studies designed to overcome the challenges of recruiting large numbers from varied demographic backgrounds, significant loss to follow up, and time or funding constraints are also likely to yield data widely applicable to IUC provision in and outside the UK.

CONCLUSION

Research is lacking on outcomes with the IUD types currently in use by young nulliparous women in the UK. Available evidence estimates a continuation rate of 81% at 12 months for the recommended standard-sized TCu 380A IUD in these women. More studies are needed to better estimate continuation rates for smaller-sized and flexible IUDs in this user group.

FIGURES

Figure 1 – PRISMA Flow Diagram

Figure 2 - TCu 380A continuation rates (excl. Otero-Flores)

Figure 3 - TCu 380A continuation rates (incl. Otero-Flores)

Figure 4 - Smaller TCu 380A continuation rates

Figure 5 - TCu 300 continuation rates

Figure 6 - TCu 200 continuation rates

Figure 7 – Nova T200 continuation rates

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COMPETING INTERESTS STATEMENT

The authors report no conflict of interest.

REPORTING STATEMENT CHECKLIST

See supplementary material 1.

DATA SHARING STATEMENT

No additional data available.

AUTHOR CONTRIBUTIONS

HA: research idea, study design, protocol, searches, first reviewer, data summary, writing - original draft, review and editing, funding application for open access publishing, project administration; AJ: second reviewer, supervision, writing – review and editing, project administration; PB: searches, writing – review and editing; MM: meta-analysis, writing – original draft, review and editing; JR: contributed to research idea, study design, protocol, funding applications, and project administration, as well as supervision and writing – review and editing. All authors approved the final version.

Ethics Approval Statement

This study does not involve human participants and does not involve animal subjects. It was therefore exempt from Research Ethics Committee review.

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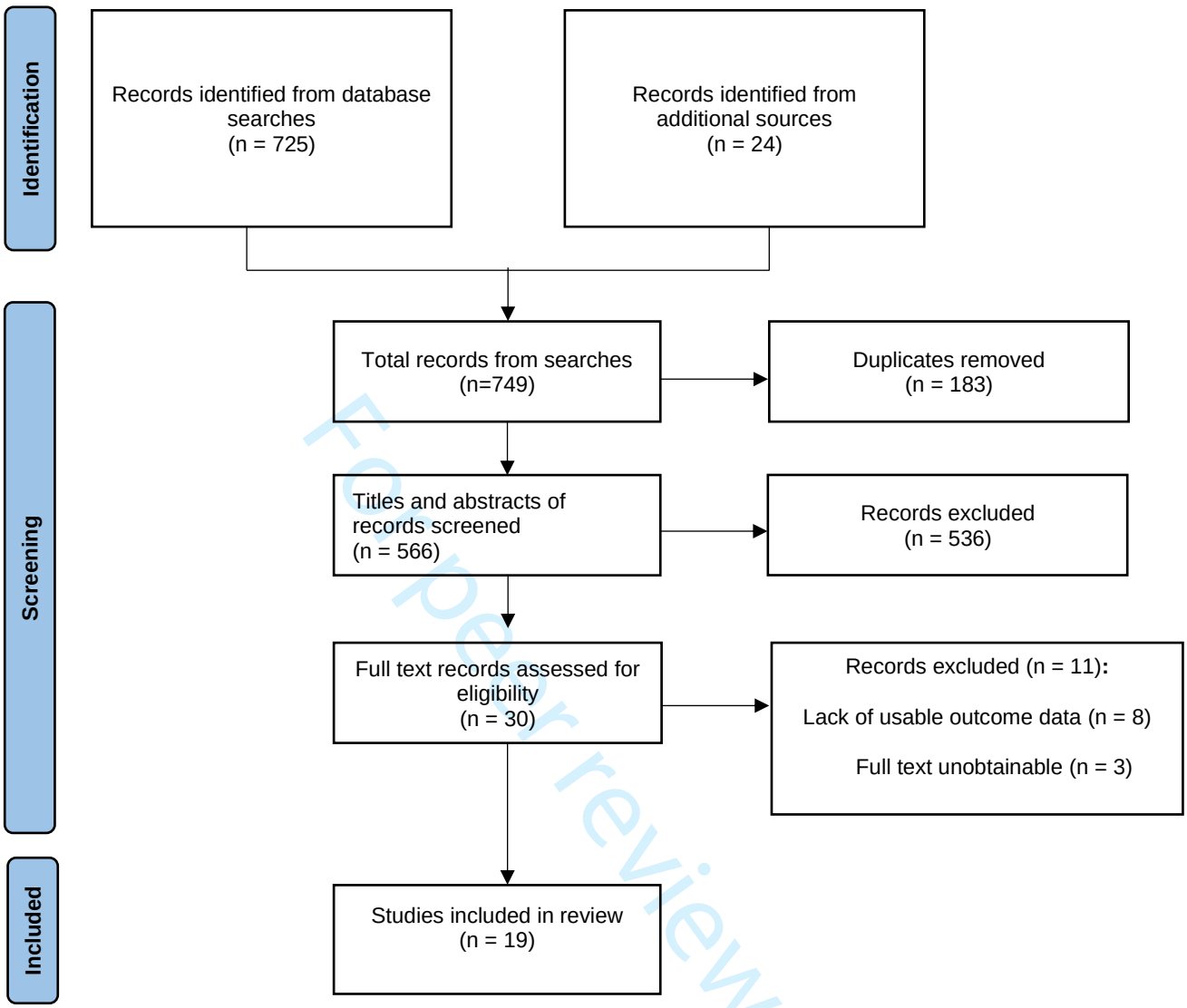

Figure 1 – PRISMA 2020 flow diagram of searches and selection of studies

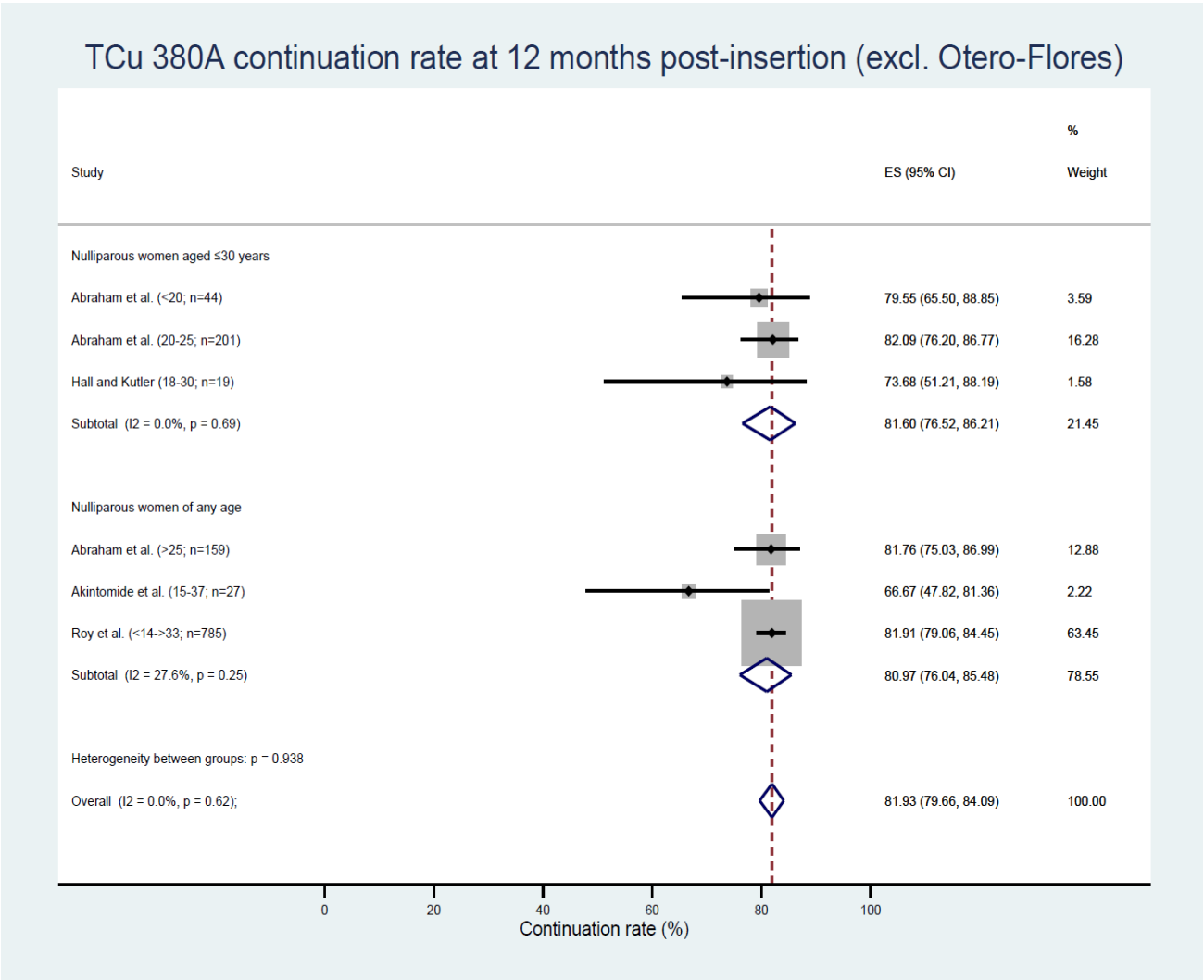

Figure 2 – TCu 380A continuation rates at 12 months (excluding Otero-Flores)

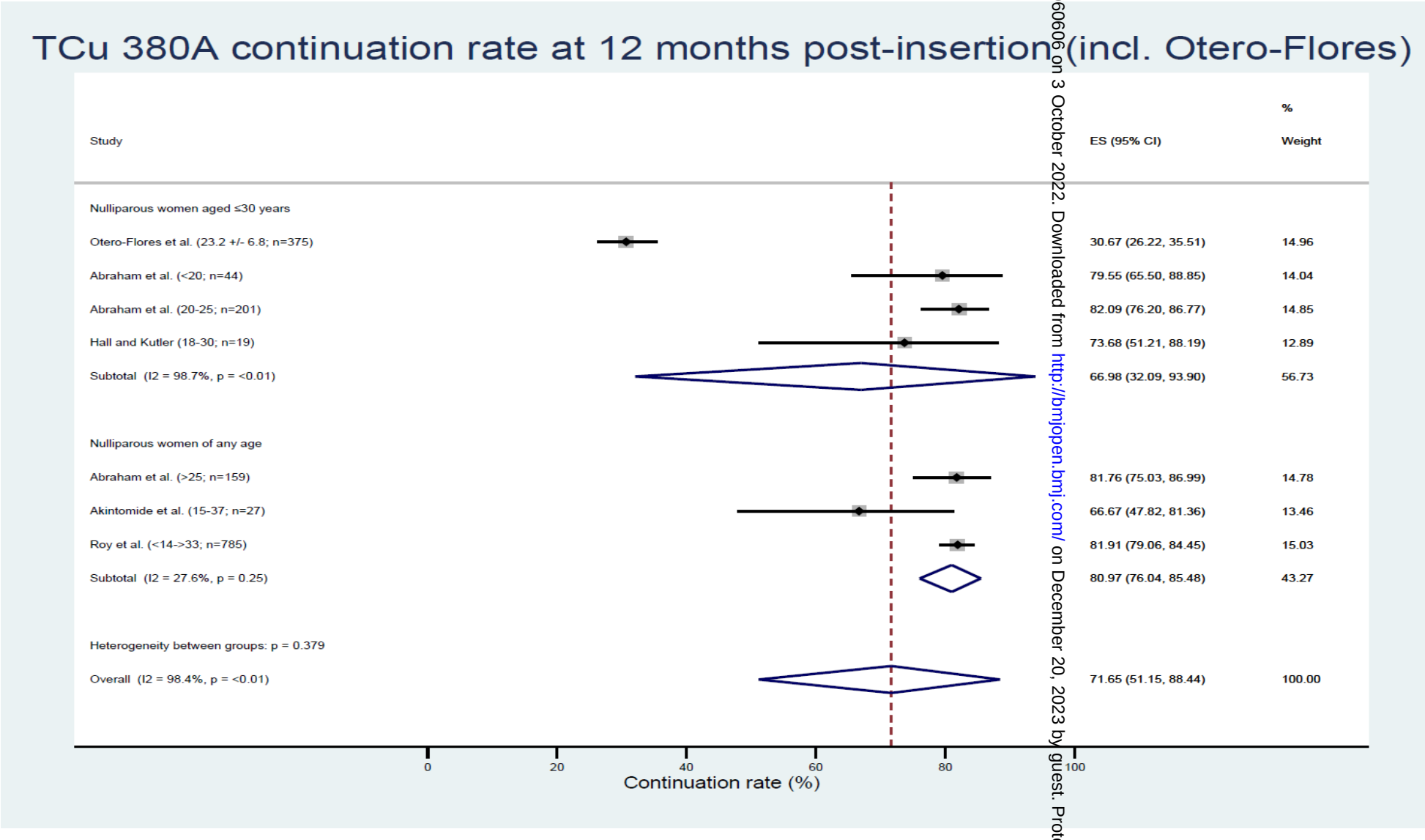

Figure 3 - TCu 380A continuation rates at 12 months (including Otero-Flores)

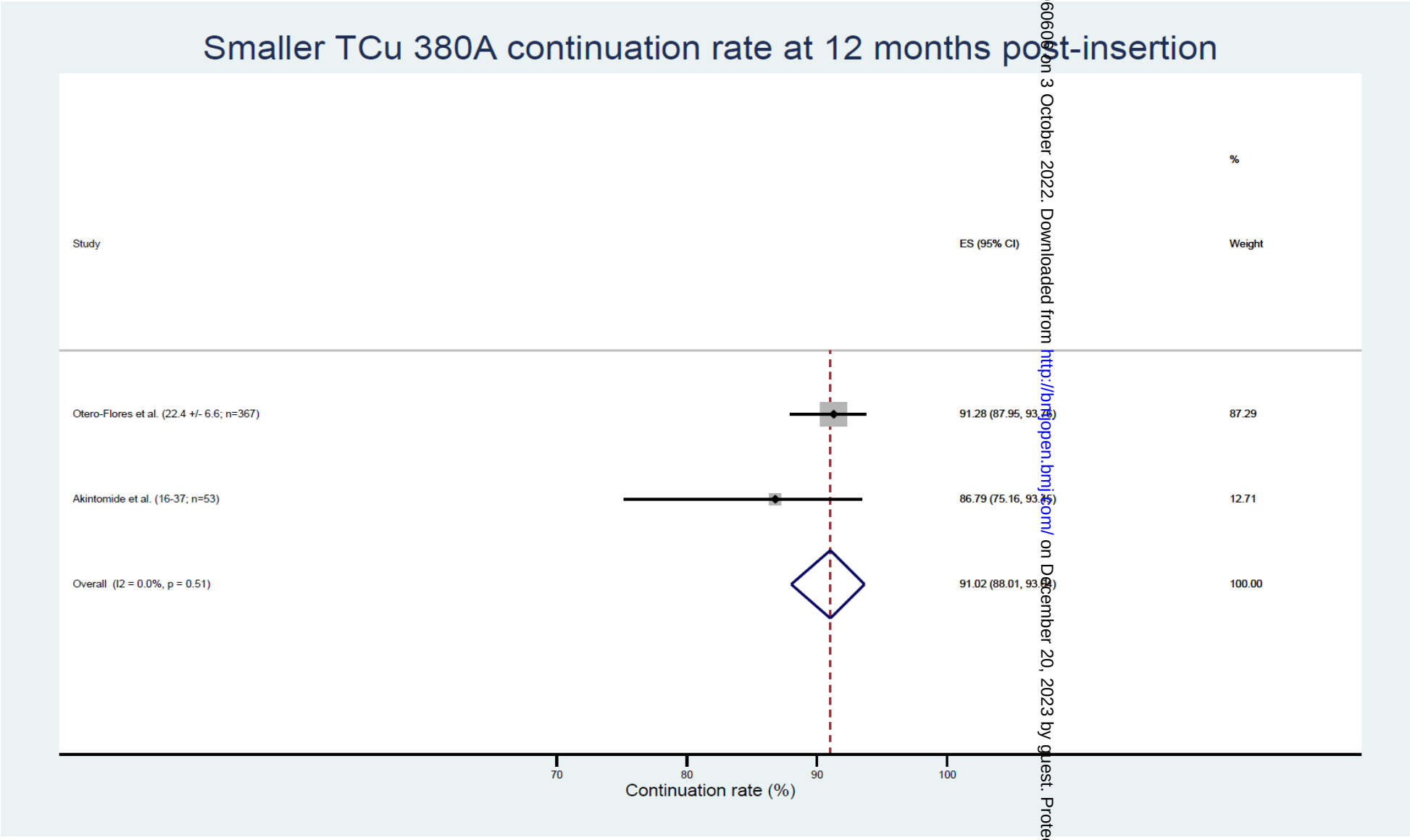

Figure 4 – Smaller TCu 380A continuation rates

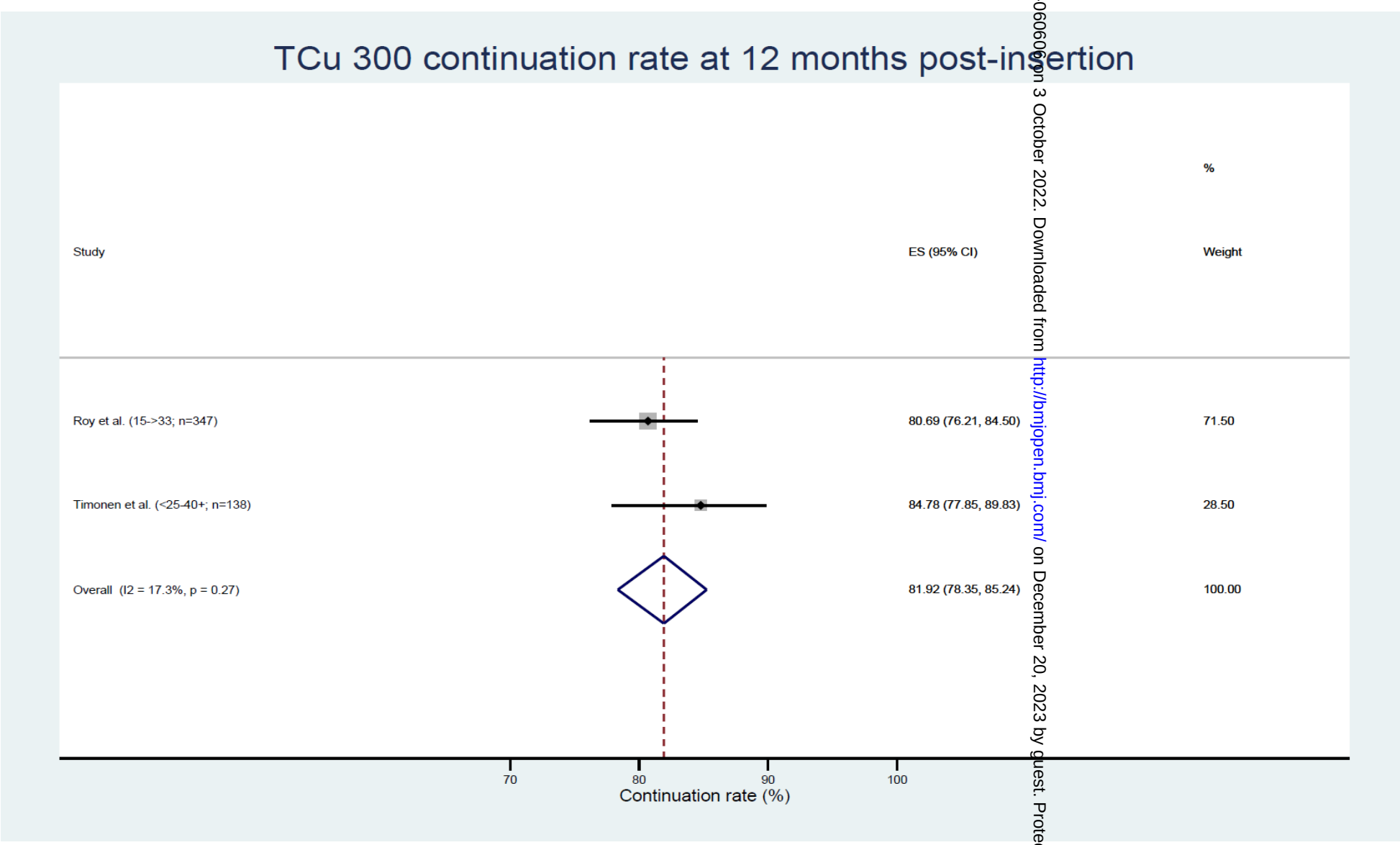

Figure 5 –TCu 300 continuation rates

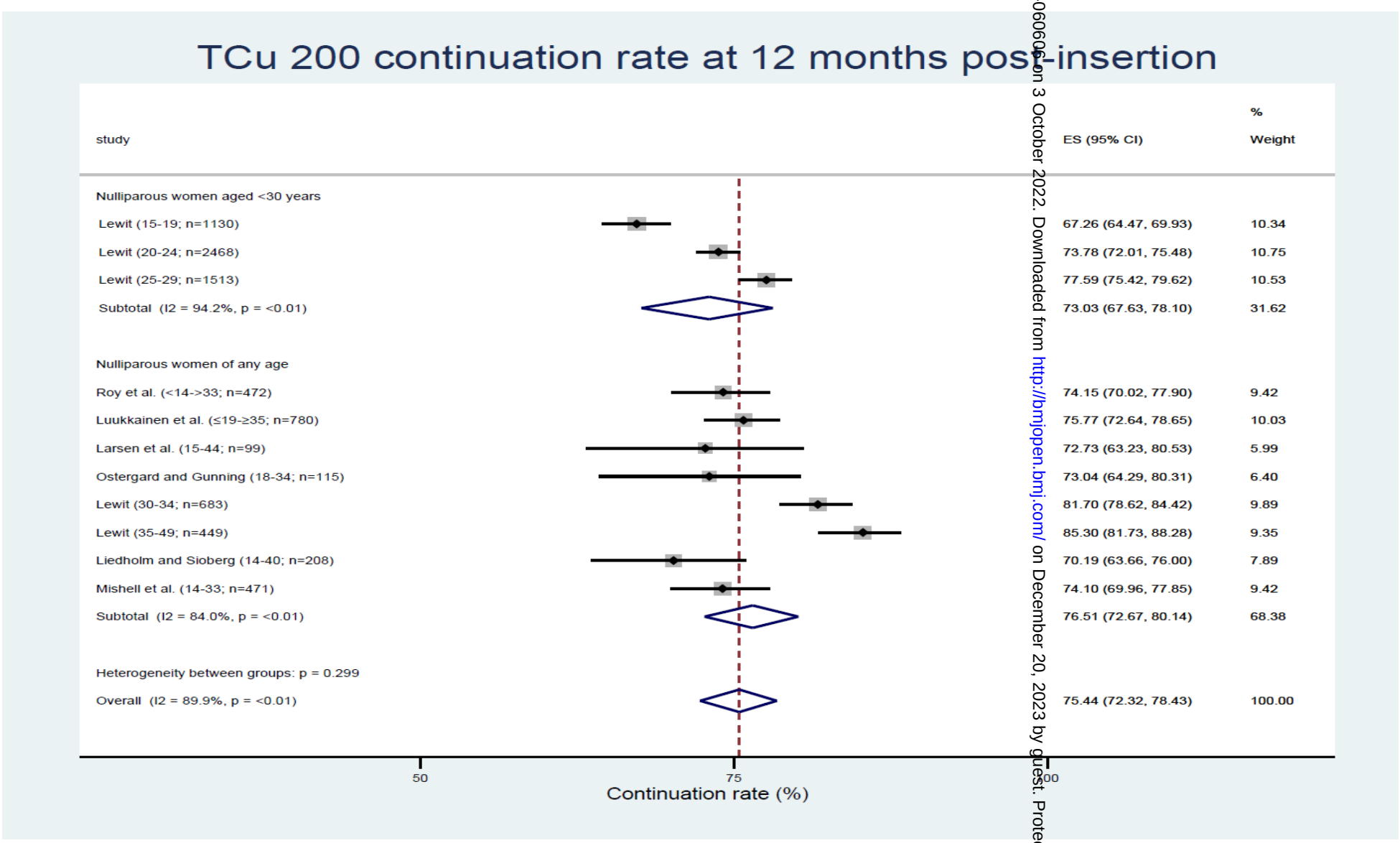

Figure 6 –TCu 200 continuation rates

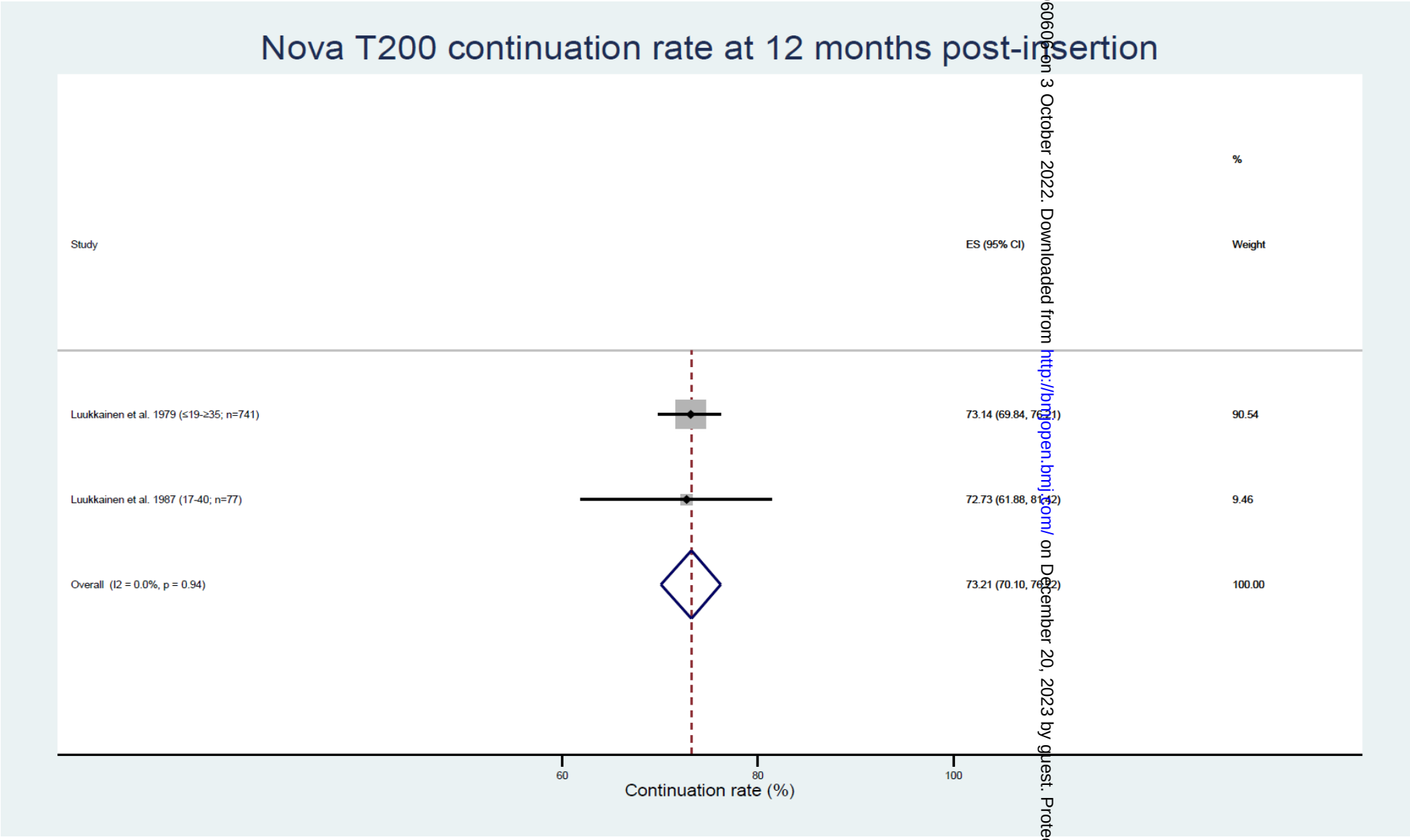

Figure 7 – Nova T200 continuation rates

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pages 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 6 Supplementary material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 6-7 Supplementary material
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 6-7 Supplementary material
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 6-7 Supplementary material
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7 Supplementary material
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7 Supplementary material
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 6-7 Supplementary material
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 6-7 Supplementary material
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7 Supplementary material

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 6-7 Supplementary material
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 6-7 Supplementary material
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pages 6-7 Supplementary material
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 6-7 Supplementary material
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 8-13 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 10 Supplementary material
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 13-9 Table 2-3 Figures 2 – 7 Supplementary material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 16-9 Figures 2 – 7 Supplementary material
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 16-9 Figures 2–7 Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 16-9 Figures 2–7 Supplementary material
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 16-9 Figures 2–7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplementary material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 19-20
	23b	Discuss any limitations of the evidence included in the review.	Page 19-20
	23c	Discuss any limitations of the review processes used.	Page 20
	23d	Discuss implications of the results for practice, policy, and future research.	Page 21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5 Supplementary material
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplementary material
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pages 5 and 8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 22
Competing interests	26	Declare any competing interests of review authors.	Page 22
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Copper intrauterine contraception discontinuation in nulliparous and young women

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin

Citation

Hannat Akintomide, Pam Barnes, Nataliya Brima, Judith Rankin. Copper intrauterine contraception discontinuation in nulliparous and young women. PROSPERO 2019 CRD42019120969 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019120969

Review question

Which copper intrauterine devices are associated with higher discontinuation rates in young and nulliparous women?

Searches

Databases [including the Cochrane Library, the Database of Abstracts and Reviews of Effects (DARE), MEDLINE (Ovid), Excerpta Medica Database (EMBASE), Turning Research into Practice (TRIP) database and National Electronic Library of Health] and relevant websites [including Bandolier, Medicines and Healthcare products Regulatory Agency, Faculty of Sexual and Reproductive Healthcare, Royal College of Obstetricians and Gynaecologists, Department of Health, Medical Defence Unions, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines, World Health Organisation and Google Scholar] will be searched using MeSH terms combined with key words for relevant articles published from 1966 to date. Reference lists of relevant articles will also be searched to identify more articles. The full texts of relevant articles will be screened, duplicates excluded and then data from selected articles included in the review.

Randomised controlled trials (RCTs) involving copper intrauterine devices (IUDs) available or comparable to those in the UK published in English will be included. Other studies that report on the main outcome (observational and qualitative studies) will be included and/or summarised if the number of RCTs eligible for inclusion are too few to answer the review question.

Key words

Copper intrauterine device related: copper intrauterine device, copper intrauterine contraceptive device, copper intrauterine contraception, copper coil, IUD

Nulliparous related: nulliparous, nulligravid, never pregnant, never delivered

Young women related: young women, adolescent, aged under, teenage

Types of study to be included

Inclusion criteria: Articles published in English on studies in women who are nulliparous and aged under 30 that involved copper intrauterine devices available, or of the same design and size to those available, in the UK.

Exclusion criteria: Articles not published in English, studies solely in parous women aged 30 or over, or that involved copper intrauterine devices not available, or not of the same design and size to those available, in the UK.

Condition or domain being studied

Copper intrauterine contraception in nulliparous and young women

Participants/population

Women who are nulliparous and aged under 30

Intervention(s), exposure(s)

Copper intrauterine devices available or comparable to those in the UK

Comparator(s)/control

Any IUD, other contraceptive or no contraception where applicable

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Context
Copper intrauterine devices (IUDs) are of various shapes, sizes, copper surface area and copper distribution on the frame of the device. There are many types of IUDs available in the UK but none shown to be associated with better outcomes in nulliparous and young women. The identification and use of those IUDs associated with less discontinuation could improve outcomes including satisfaction and continuation rates of intrauterine contraception in nulliparous and younger women.

Main outcome(s)
Copper intrauterine contraception discontinuation rates in nulliparous and young women based on type of IUD

Timing and effect measures

Additional outcome(s)
Reasons for IUD discontinuation

Timing and effect measures

Data extraction (selection and coding)
The abstracts of published articles obtained from the literature and websites searches will be reviewed by two authors to assess eligibility for inclusion in the systematic review based on the inclusion/exclusion criteria. All retrieved full texts of published articles will be reviewed to agree which studies to include in the systematic review, with disagreements resolved by the third author. All retrieved articles to be included in the systematic review will undergo a quality assessment using a risk of bias tool applicable to the type of study.

Main data to be extracted:

type of copper intrauterine device (IUD)

age of women

gravidity/parity of women

place/time of IUD insertion

IUD discontinuation rate(s)

reason(s) for IUD discontinuation

Risk of bias (quality) assessment
All retrieved articles to be included in the systematic review will undergo a quality assessment. One author will complete the inclusion criteria checklist while the second author will review the checklist, with disagreements resolved by the third author/consensus. Retrieved articles with a high risk of bias will be excluded from the systematic review.

Strategy for data synthesis
Data from the included studies will be extracted using a standardised form by one author while the second author will check these. Disagreements will be resolved by a further review of the study with the third author and consensus. One author will enter the extracted data into Review Manager (RevMan®) Software while the second author will again check these for accuracy. It is planned that aggregate data will be used. However, individual data on the intervention and population of interest (IUDs in nulliparous and young women aged under 30) will be extracted where studies have reported on this subgroup their outcomes in conjunction with other population subgroups or study outcomes.
A quantitative synthesis is planned based on the expected homogeneity of the data to be obtained for the main outcome to be studied. This homogeneous data will be combined for meta-analysis. Heterogeneous

data, some of which is expected to be obtained on the additional outcome, will be narratively synthesised.

Analysis of subgroups or subsets
IUDs of same size and design will be grouped and discontinuation rates presented based on IUD type.

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Nil

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England

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Subject indexing assigned by CRD

Subject index terms
Contraception; Copper; Female; Humans; Intrauterine Devices; Parity; Pregnancy

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07 February 2019

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

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National Institute for Health Research

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

07 February 2019

Table – Search Strategies

Databases and additional sources search	Search term(s) used	Limits	Records identified
Allied and Complementary Medicine (AMED) British Nursing Index (BNI) Cumulative Index to Nursing and Allied Health Literature (CINAHL) Excerpta Medica Database (EMBASE) Nursing and Allied Health Professionals Database (EMCARE) Health Management Information Consortium (HMIC) General Medical Database (MEDLINE) Psychology and Allied Fields (PsychINFO) PubMed	(copper intrauterine).ti,ab OR (copper intrauterine device).ti,ab OR (copper coil).ti,ab OR (copper IUD).ti,ab OR (copper T).ti,ab	Title, Abstract English language	**725**
The Cochrane Library Database of Abstracts and Reviews of Effects (DARE) Turning Research into Practice (TRIP) Bandolier National Electronic Library of Health Medicines and Healthcare products Regulatory Agency (MHRA) Faculty of Sexual and Reproductive Healthcare (FSRH) Royal College of Obstetricians and Gynaecologists (RCOG) Department of Health National Institute for Health and Care Excellence (NICE) Scottish Intercollegiate Guidelines, World Health Organisation (WHO)	'copper intrauterine'	-	**22**
Google Scholar	'copper intrauterine device young nulliparous'	-	

TCu 380A continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(81.60% (95% CI 76.52-86.21%))**
Excluding Abraham et al. (<20)	82.04% (95% CI 76.48-87.04%)
Excluding Abraham et al. (20-25)	78.01% (95% CI 66.60-87.74%)
Excluding Hall and Kutler (18-30)	81.83% (95% CI 76.66-86.49%)
Subgroup 2 (Nulliparous women of any age)	**(80.97% (95% CI 76.04-85.48%))**
Excluding Abraham et al. (>25)	81.99% (95% CI 79.19-84.63%)
Excluding Akintomide et al. (15-37)	81.94% (95% CI 79.41-84.34%)
Excluding Roy et al. (14-33)	80.12% (95% CI 73.92-85.70%)
Overall effect size (all studies)	**(81.93% (95% CI 79.66-84.09%))**
Excluding Abraham et al. (<20)	81.84% (95% CI 79.13-84.40%)
Excluding Abraham et al. (20-25)	81.44% (95% CI 78.16-84.53%)
Excluding Hall and Kutler (18-30)	81.87% (95% CI 79.60-84.03%)
Excluding Abraham et al. (>25)	81.57% (95% CI 78.38-84.58%)
Excluding Akintomide et al. (15-37)	82.14% (95% CI 79.87-84.31%)
Excluding Roy et al. (14-33)	80.92% (95% CI 76.93-84.64%)

TCu 200 continuation at 12 months post-insertion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(73.03% (95% CI 67.63-78.10%))**
Excluding Lewit (15-19)	75.26% (95% CI 73.90-76.59%)
Excluding Lewit (20-24)	73.33% (95% CI 71.62-75.00%)
Excluding Lewit (25-29)	71.78% (95% CI 70.30-73.24%)
Subgroup 2 (Nulliparous women of any age)	**(76.51% (95% CI 72.67-80.14%))**
Excluding Roy et al. (14-33)	76.83% (95% CI 72.49-80.91%)
Excluding Luukkainen et al. (19-35)	76.53% (95% CI 71.86-80.91%)
Excluding Larsen et al. (15-44)	76.85% (95% CI 72.79-80.67%)
Excluding Ostergard and Gunning (18-34)	76.84% (95% CI 72.76-80.69%)
Excluding Lewit (30-34)	75.59% (95% CI 71.42-79.54%)
Excluding Lewit (35-49)	75.20% (95% CI 71.98-78.29%)
Excluding Liedholm and Sioberg (14-40)	77.32% (95% CI 73.40-81.01%)
Excluding Mishell et al. (14-33)	76.84% (95% CI 72.51-80.91%)
Overall effect size (all studies)	**(75.44% (95% CI 72.32-78.43%))**
Excluding Lewit (15-19)	76.43% (95% CI 73.71-79.04%)
Excluding Lewit (20-24)	75.59% (95% CI 71.81-79.17%)
Excluding Lewit (25-29)	76.16% (95% CI 71-60-78.56%)
Excluding Roy et al. (14-33)	75.56% (95% CI 72.16-78.81%)
Excluding Luukkainen et al. (19-35)	75.38% (95% CI 71.89-78.72%)
Excluding Larsen et al. (15-44)	75.60% (95% CI 72.34-78.70%)
Excluding Ostergard and Gunning (18-34)	75.59% (95% CI 72.33-78.71%)
Excluding Lewit (30-34)	74.72% (95% CI 71.59-77.73%)

Excluding Lewit (35-49)	74.37% (95% CI 71.53-77.10%)
Excluding Liedholm and Sioberg (14-40)	75.87% (95% CI 72.61-78.98%)
Excluding Mishell et al. (14-33)	75.56% (95% CI 72.16-78.81%)

TCu 200 discontinuation at 12 months due to pain/bleeding – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(7.05% (95% CI 5.59-8.65%))**
Excluding Lewit (15-19)	7.31% (95% CI 6.52-8.14%)
Excluding Lewit (20-24)	6.31% (95% CI 5.41-7.27%)
Excluding Lewit (25-29)	7.88% (95% CI 7.02-8.78%)
Subgroup 2 (Nulliparous women of any age)	**(12.77% (95% CI 8.48-17.78%))**
Excluding Roy et al. (14-33)	13.10% (95% CI 8.10-19.06%)
Excluding Luukkainen et al. (19-35)	11.02% (95% CI 8.41-13.92%)
Excluding Larsen et al. (15-44)	12.40% (95% CI 7.87-17.76%)
Excluding Ostergard and Gunning (18-34)	12.86% (95% CI 8.20-18.35%)
Excluding Lewit (30-34)	13.61% (95% CI 8.83-19.22%)
Excluding Lewit (35-49)	13.79% (95% CI 9.10-19.25%)
Excluding Liedholm and Sioberg (14-40)	12.08% (95% CI 7.56-17.45%)
Excluding Mishell et al. (14-33)	13.13% (95% CI 8.13-19.08%)
Overall effect size (all studies)	**(10.87% (95% CI 7.98-14.15%))**
Excluding Lewit (15-19)	11.37% (95% CI 8.08-15.12%)
Excluding Lewit (20-24)	11.23% (95% CI 7.70-15.32%)
Excluding Lewit (25-29)	11.52% (95% CI 8.34-15.14%)
Excluding Roy et al. (14-33)	10.90% (95% CI 7.77-14.47%)
Excluding Luukkainen et al. (19-35)	9.32% (95% CI 7.62-11.17%)
Excluding Larsen et al. (15-44)	10.51% (95% CI 7.58-13.86%)
Excluding Ostergard and Gunning (18-34)	10.78% (95% CI 7.77-14.20%)
Excluding Lewit (30-34)	11.23% (95% CI 8.01-14.92%)
Excluding Lewit (35-49)	11.34% (95% CI 8.17-14.94%)
Excluding Liedholm and Sioberg (14-40)	10.26% (95% CI 7.40-13.53%)
Excluding Mishell et al. (14-33)	10.92% (95% CI 7.78-14.50%)

TCu 200 discontinuation at 12 months due to expulsion – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(10.52% (95% CI 7.17-14.41%))**
Excluding Lewit (15-19)	8.59% (95% CI 7.74-9.48%)
Excluding Lewit (20-24)	11.21% (95% CI 10.03-12.44%)
Excluding Lewit (25-29)	10.36% (95% CI 9.38-11.38%)
Subgroup 2 (Nulliparous women of any age)	**(4.93% (95% CI 2.93-7.39%))**
Excluding Roy et al. (14-33)	4.85% (95% CI 2.57-7.78%)
Excluding Luukkainen et al. (19-35)	4.17% (95% CI 2.68-5.96%)
Excluding Larsen et al. (15-44)	4.92% (95% CI 2.79-7.58%)
Excluding Ostergard and Gunning (18-34)	4.80% (95% CI 2.69-7.46%)
Excluding Lewit (30-34)	4.74% (95% CI 2.41-7.76%)
Excluding Lewit (35-49)	5.24% (95% CI 3.03-7.99%)
Excluding Liedholm and Sioberg (14-40)	5.84% (95% CI 3.95-8.07%)

Excluding Mishell et al. (14-33)	4.85% (95% CI 2.57-7.77%)
Overall effect size (all studies)	**(6.44% (95% CI 4.49-8.69%))**
Excluding Lewit (15-19)	5.76% (95% CI 4.14-7.61%)
Excluding Lewit (20-24)	6.16% (95% CI 3.87-8.93%)
Excluding Lewit (25-29)	6.16% (95% CI 3.96-8.79%)
Excluding Roy et al. (14-33)	6.55% (95% CI 4.47-8.99%)
Excluding Luukkainen et al. (19-35)	6.01% (95% CI 3.98-8.42%)
Excluding Larsen et al. (15-44)	6.54% (95% CI 4.51-8.91%)
Excluding Ostergard and Gunning (18-34)	6.46% (95% CI 4.43-8.83%)
Excluding Lewit (30-34)	6.47% (95% CI 4.36-8.95%)
Excluding Lewit (35-49)	6.87% (95% CI 4.87-9.18%)
Excluding Liedholm and Sioberg (14-40)	7.29% (95% CI 5.39-9.45%)
Excluding Mishell et al. (14-33)	6.55% (95% CI 4.47-8.99%)

TCu 200 discontinuation at 12 months due to pregnancy – sensitivity analysis

Subgroup 1 (Nulliparous women aged <30 years)	**(2.19% (95% CI 1.47-3.05%))**
Excluding Lewit (15-19)	2.27% (95% CI 1.82-2.75%)
Excluding Lewit (20-24)	1.83% (95% CI 1.35-2.39%)
Excluding Lewit (25-29)	2.63% (95% CI 2.13-3.18%)
Subgroup 2 (Nulliparous women of any age)	**(1.15% (95% CI 0.54-1.95%))**
Excluding Roy et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Excluding Luukkainen et al. (19-35)	0.96% (95% CI 0.38-1.75%)
Excluding Larsen et al. (15-44)	1.18% (95% CI 0.53-2.05%)
Excluding Ostergard and Gunning (18-34)	1.31% (95% CI 0.65-2.16%)
Excluding Lewit (30-34)	1.35% (95% CI 0.70-2.18%)
Excluding Lewit (35-49)	1.31% (95% CI 0.62-2.20%)
Excluding Liedholm and Sioberg (14-40)	1.00% (95% CI 0.42-1.78%)
Excluding Mishell et al. (14-33)	1.07% (95% CI 0.40-1.99%)
Overall effect size (all studies)	**(1.49% (95% CI 0.96-2.13%))**
Excluding Lewit (15-19)	1.39% (95% CI 0.81-2.09%)
Excluding Lewit (20-24)	1.34% (95% CI 0.83-1.94%)
Excluding Lewit (25-29)	1.48% (95% CI 0.87-2.22%)
Excluding Roy et al. (14-33)	1.46% (95% CI 0.89-2.16%)
Excluding Luukkainen et al. (19-35)	1.40% (95% CI 0.83-2.09%)
Excluding Larsen et al. (15-44)	1.53% (95% CI 0.98-2.19%)
Excluding Ostergard and Gunning (18-34)	1.62% (95% CI 1.07-2.26%)
Excluding Lewit (30-34)	1.69% (95% CI 1.18-2.29%)
Excluding Lewit (35-49)	1.64% (95% CI 1.10-2.28%)
Excluding Liedholm and Sioberg (14-40)	1.41% (95% CI 0.88-2.06%)
Excluding Mishell et al. (14-33)	1.46% (95% CI 0.89-2.16%)

Table – Characteristics of studies excluded following full text assessment

Study / Authors	Year	Country	Study Design	Study Objectives	Reasons for Exclusion
Akintomide et al[5]	2021	Austria, Finland, Germany, Poland, Sweden, UK	Prospective cohort	Secondary analysis of continuation, unwanted effects and cost consequences at 1 year in IUD users ≤30 in the European Active Surveillance Study for Intrauterine Devices	Undifferentiable results - IUD type categories based on IUD characteristics rather than brand or name of IUD
Garbers et al[20]	2013	USA	Retrospective records review	Prevalence and predictors of IUD discontinuation at 6 months in 306 Cu T380A users	Undifferentiable results; varied duration; 23 excluded from continuation analysis
Goldstuck[21]	1980	UK	Prospective cohort (selected)	Clinical evaluation of the combined multiload copper 250-mini IUD in selected nulliparous women	Undifferentiable results; disparity between data in tables and text
Hindle[27]	1978	Unable to confirm		Clinical evaluation and follow-up on 3,829 IUD procedures	Full text unobtainable
Lete et al[22]	1998	Spain	Prospective cross-sectional	Evaluation of IUD use in nulliparous women compared to parous women over a 12-year period	Data reported as incidence of events rather than rates
Ogedengbe et al[23]	1991	Nigeria	Prospective cohort	A comparison efficacy and discontinuation at 1 year of multiload and copper-T IUDs sequentially assigned to users	Parity of participants not detailed (mean parity 4); only one nulliparous participant
Patnaik[28]	2003	India	Unable to confirm	Uptake, satisfaction, retention and reasons for discontinuation of the copper T IUD	Full text unobtainable
Petersen et al[29]	1991	Unable to confirm	RCT – double blind	Significance of endometrial cavity length in the clinical performance of IUDs in nulligravidae	Full text unobtainable
Phillips et al[24]	2017	USA	Retrospective records review	Comparison of continuation and performance of levonorgestrel and copper intrauterine devices over 5 years	Undifferentiable results
Sivin and Tatum[25]	1981	USA	Prospective cohort	Clinical performance of the TCu 380A IUD over 4 years	Undifferentiable results
Teal et al[26]	2015	USA	Retrospective records review	Evaluation of the success and safety of intrauterine device (IUD) placement in adolescents based on age and parity	Undifferentiable results

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Table – Quality Assessment of Included Studies Using the Mixed Methods Appraisal Tool (MMAT) version 2018

Study / Authors	*Design Category*	*Responses to MMAT Questions (and Scores: Yes (1) / No (0) / Can't Tell (0)*							
		Screening 1	**Screening 2**	**Appraisal 1**	**Appraisal 2**	**Appraisal 3**	**Appraisal 4**	**Appraisal 5**	**Total**
Abraham et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Akintomide et al 2019	Quantitative, non-randomised	yes	yes	yes	yes	no	yes	yes	6
Allonen et al 1980	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Elkhateeb et al 2020	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Fugere 1990	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Hall and Kutler 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Kaislasuo et al 2015	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Larsen et al 1981	Quantitative, randomised	yes	yes	can't tell	yes	yes	no	yes	5
Lewit 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Liedholm and Sjoberg 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Luukkainen et al 1979	Quantitative, randomised	yes	yes	can't tell	yes	yes	yes	yes	6
Luukkainen et al 1987	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Mishell et al 1973	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Nygren et al 1981	Quantitative, randomised	yes	yes	yes	yes	yes	yes	yes	7
Ostergard and Gunning 1979	Quantitative, randomised	yes	yes	yes	can't tell	yes	no	yes	5
Otero-Flores et al 2003	Quantitative, randomised	yes	yes	yes	yes	yes	no	yes	6
Roy et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7
Sivin and Stern 1979	Quantitative, randomised	yes	yes	can't tell	can't tell	yes	yes	yes	5
Timonen et al 1974	Quantitative, non-randomised	yes	yes	yes	yes	yes	yes	yes	7

Tau² Values for Heterogeneity of Included Studies

IUD type	Tau² Values for Heterogeneity of Included Studies for Continuation Rates		
	Nulliparous women aged <30	**Nulliparous women of any age**	**Overall effect size (all studies)**
TCu 380A excluding Otero- Flores data	0.0[a] [19, 34]	0.005 [19, 30, 45]	0.0 [19, 30, 34, 45]
TCu 380A including Otero- Flores data	0.487 [19, 34, 44]	0.005 [19, 30, 44, 45]	0.299 [19, 30, 34, 44, 45]
Smaller TCu 380A[b]	not applicable – only one study group	0.0 [30, 44]	0.0 [30, 44]
TCu 300	not applicable – no study	0.0 [45, 47]	0.0 [45, 47]
TCu 200	0.010 [37]	0.012 [37-39, 41, 43, 45]	0.012 [37-39, 41, 43, 45]
Nova T200	not applicable – no study	0.0 [39, 40]	0.0 [39, 40]
	Tau² Values for Heterogeneity of Included Studies for Discontinuation Rates		
TCu 200 discontinuation due to bleeding/pain	0.001 [37]	0.036 [36-39, 41, 43, 45]	0.025 [36-39, 41, 43, 45]
TCu 200 discontinuation due to expulsion	0.010 [37]	0.018 [36-39, 41, 43, 45]	0.018 [36-39, 41, 43, 45]
TCu 200 discontinuation due to pregnancy	0.002 [37]	0.005 [36-39, 41, 43, 45]	0.004 [36-39, 41, 43, 45]

a – includes women aged 30 from Hall and Kutler study data; b – TCu 380A Nul/Mini TT380 Slimline IUDs

Supplementary material – Doi plots

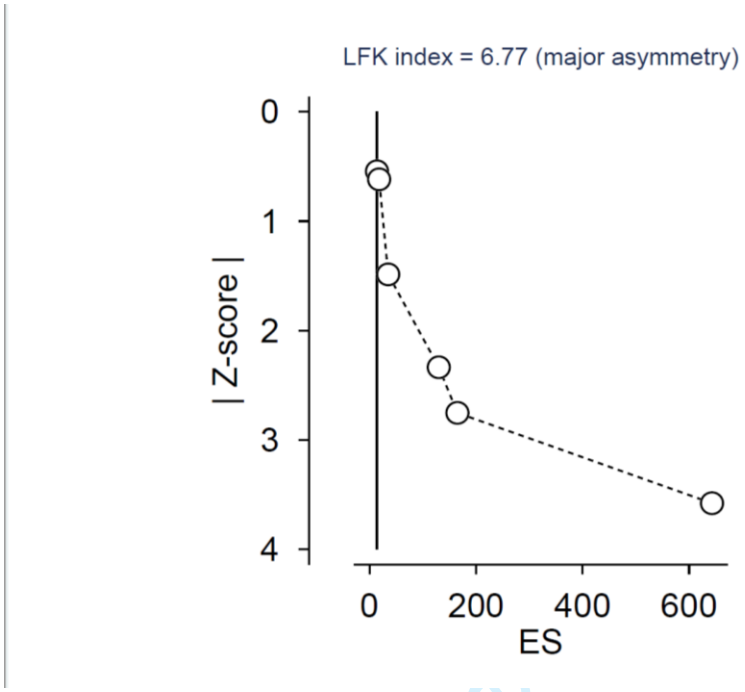

Figure 1 - Doi plot for TCu 380A continuation at 12 months

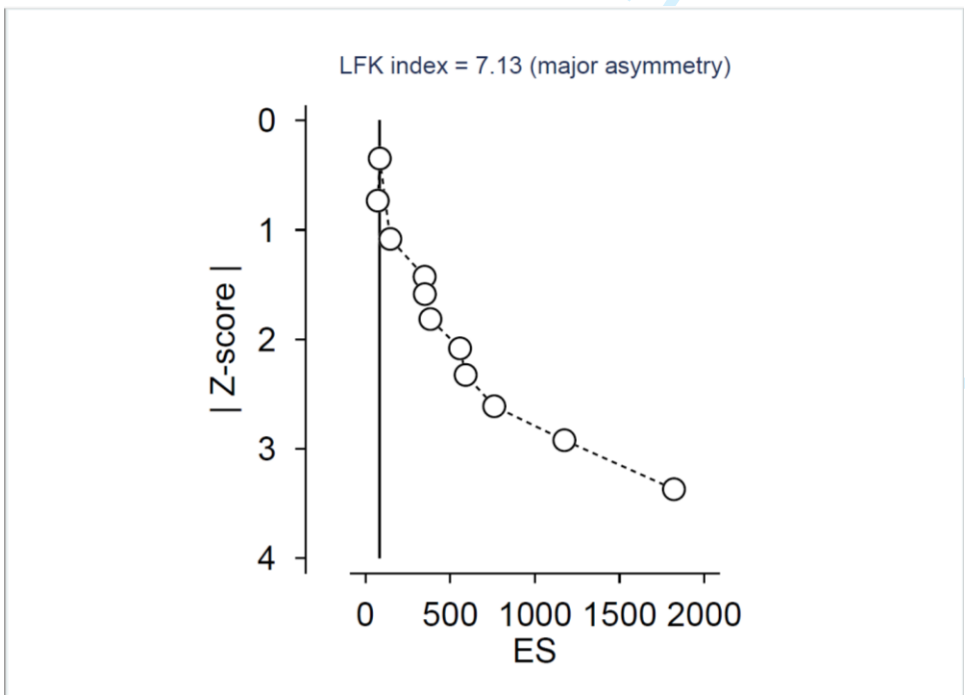

Figure 2 – Doi plot for TCu 200 continuation at 12 months

Supplementary material – Doi plots

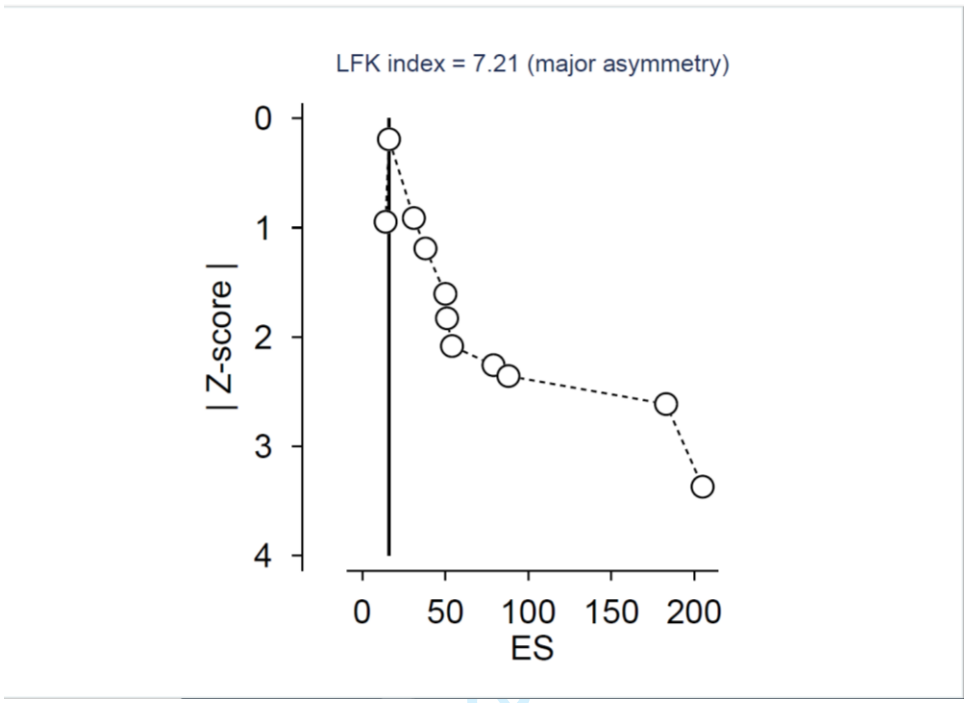

Figure 3 – Doi plot for TCu 200 discontinuation at 12 months due to bleeding/pain

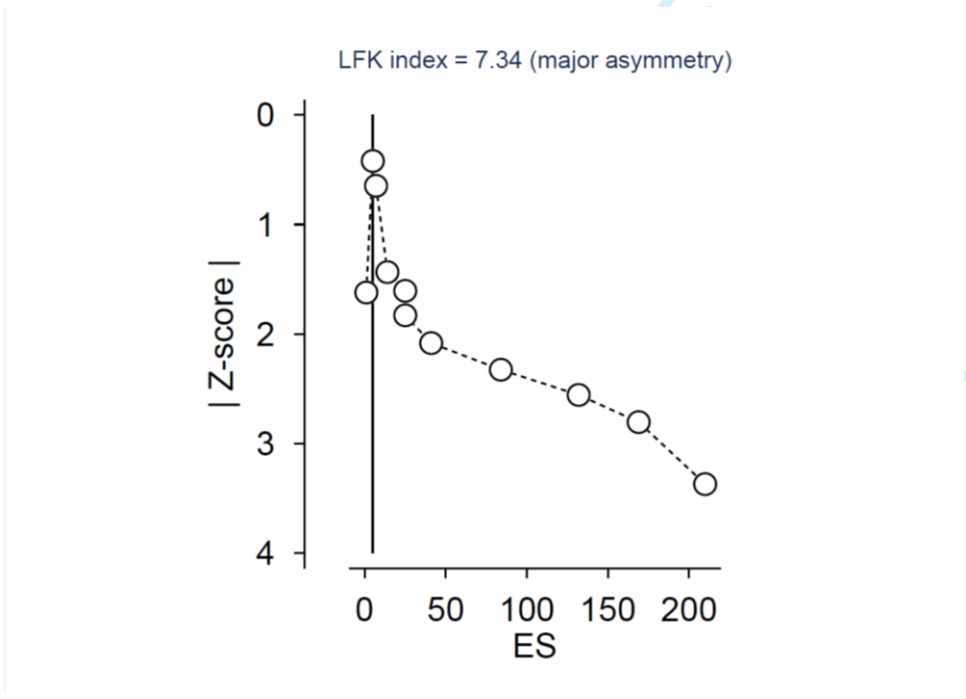

Figure 4 – Doi plot for TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – Doi plots

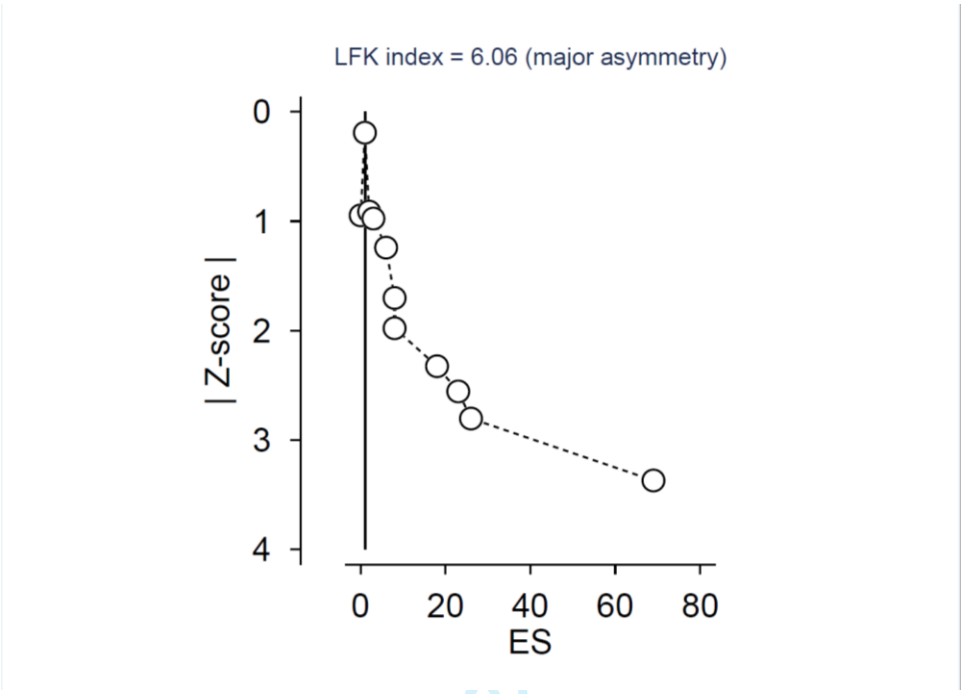

Figure 5 – Doi plot for TCu 200 discontinuation due to pregnancy

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

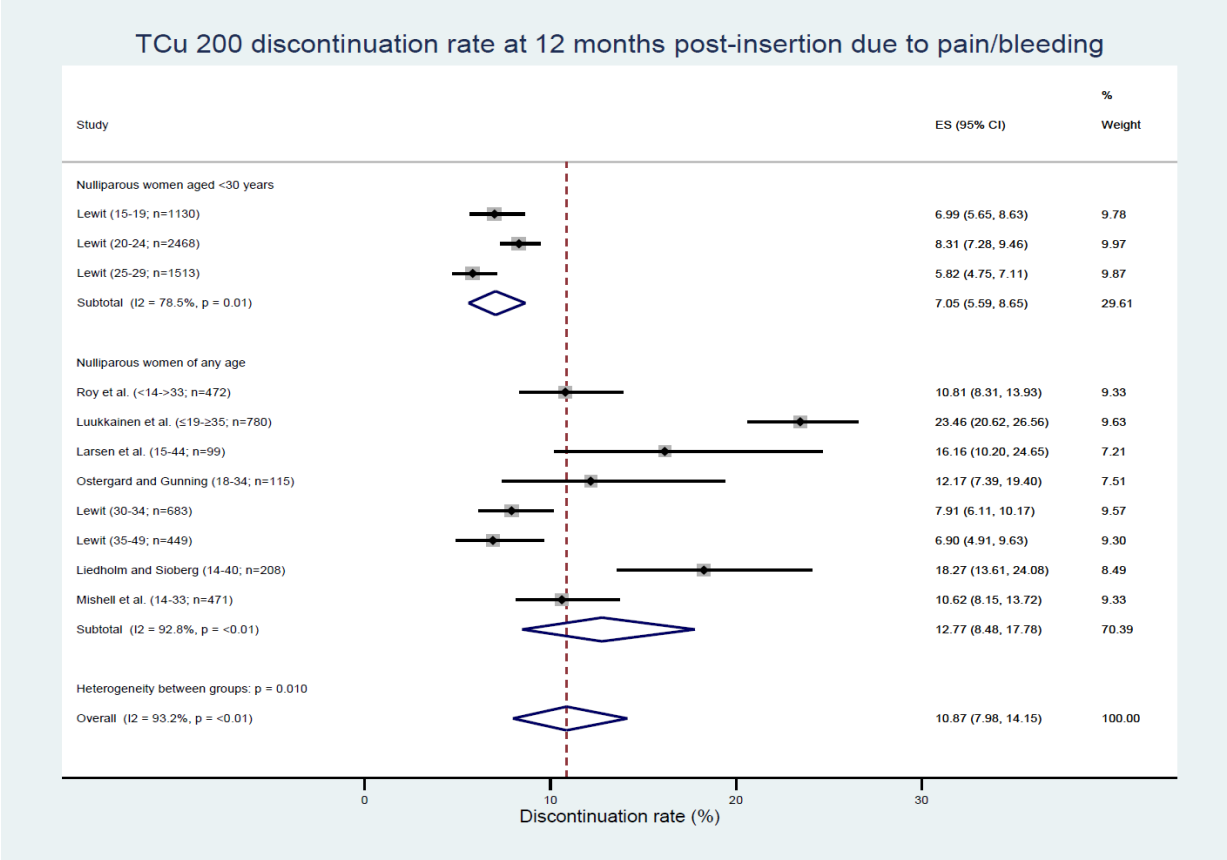

Figure 1 - TCu 200 discontinuation at 12 months due to pain/bleeding

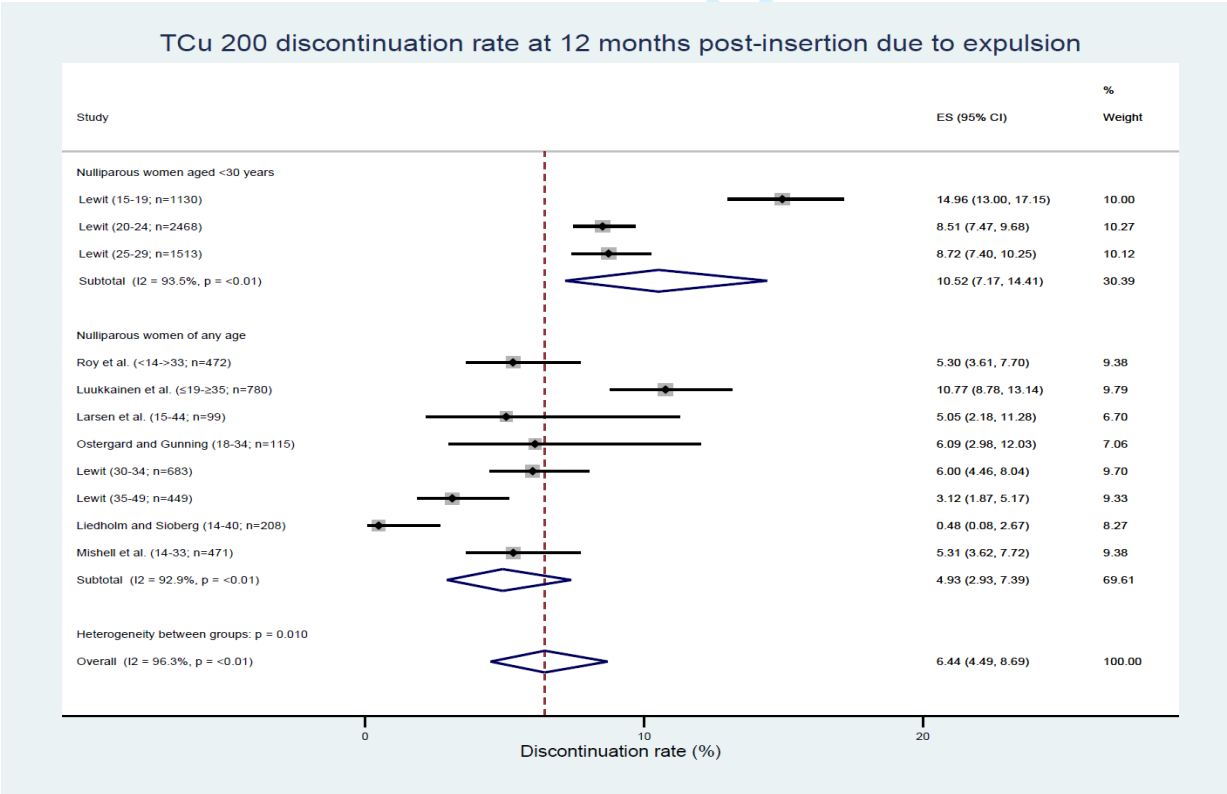

Figure 2 – TCu 200 discontinuation at 12 months due to expulsion

Supplementary material – TCu 200 discontinuation rates due to pain/bleeding, expulsion and pregnancy

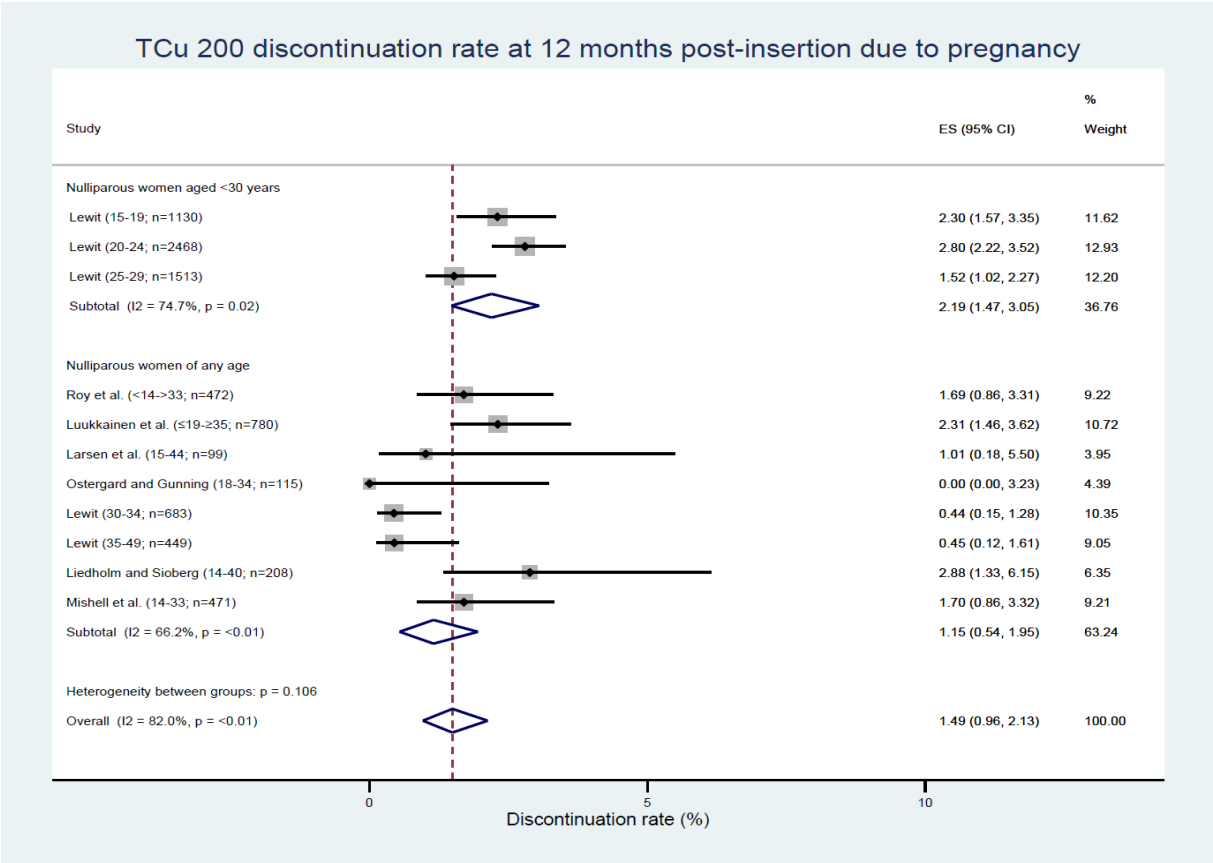

Figure 3 – TCu 200 discontinuation at 12 months due to pregnancy