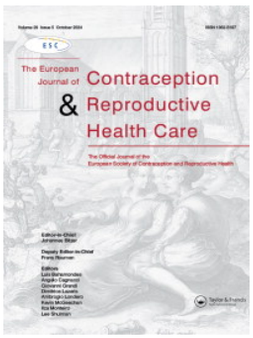

The European Journal of Contraception & Reproductive Health Care

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iejc20

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To cite this article: Shayesteh Jahanfar, Julie Mortazavi, Amy Lapidow, Cassandra Cu, Jude Al Abosy, Hartman Ciana, Katherine Morris, Meredith Steinfeldt, Olivia Maurer, Jiang Bohang, Rajkumari Anjali Oberoi & Moazzam Ali (2024) Assessing the impact of hormonal contraceptive use on menstrual health among women of reproductive age – a systematic review, The European Journal of Contraception & Reproductive Health Care, 29:5, 193-223, DOI: 10.1080/13625187.2024.2373143

To link to this article: https://doi.org/10.1080/13625187.2024.2373143

THE EUROPEAN JOURNAL OF CONTRACEPTION & REPRODUCTIVE HEALTH CARE
2024, VOL. 29, NO. 5, 193–223
https://doi.org/10.1080/13625187.2024.2373143

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REVIEW ARTICLE

Assessing the impact of hormonal contraceptive use on menstrual health among women of reproductive age – a systematic review

Shayesteh Jahanfar[a], Julie Mortazavi[b], Amy Lapidow[b], Cassandra Cu[c], Jude Al Abosy[b], Hartman Ciana[b], Katherine Morris[b], Meredith Steinfeldt[b], Olivia Maurer[c], Jiang Bohang[b], Rajkumari Anjali Oberoi[c] and Moazzam Ali[d]

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ABSTRACT

Background: Contraceptive methods are well-established in their ability to prevent pregnancy and increase individual agency in childbearing. Evidence suggests that contraceptives can also be used to treat adverse conditions associated with menstruation, including abnormal and prolonged uterine bleeding, heavy menstrual bleeding, painful menstruation, endometriosis, uterine fibroids, and premenstrual dysphoric disorders.

This review investigates the effects of contraceptive techniques such as contraceptive pills, and long-acting reversible contraceptives (e.g. intrauterine devices, implants) on menstrual morbidity.

Methods: Over ten databases with no geographical boundaries were searched from inception until October 2023. Study designs were one of the following types to be included: parallel or cluster randomised controlled trials, controlled clinical trials, controlled before and after studies, interrupted time series studies, cohort or longitudinal analyses, regression discontinuity designs, and case-control studies. Ten team members screened the papers in pairs with a Kappa score of more than 7, and Covidence was used. Conflicts were resolved by discussion, and the full papers were divided among the reviewers to extract the data from eligible studies.

Results: Hormonal contraceptives are considered a well-tolerated, non-invasive, and clinically effective treatment for abnormal and prolonged uterine bleeding, heavy menstrual bleeding, painful menstruation, endometriosis, uterine fibroids, and premenstrual dysphoric disorders. Our studies investigating quality of life or well-being in women with heavy menstrual bleeding, endometriosis, or uterine fibroids have found improvements in all dimensions assessed.

Conclusions: Hormonal contraceptives significantly reduce pain, symptom severity, and abnormal bleeding patterns associated with women who suffer from heavy menstrual bleeding, endometriosis, and uterine fibroids.

SHORT CONDENSATION

Hormonal contraceptives significantly reduce pain, symptom severity, and abnormal bleeding patterns associated with women who suffer from heavy menstrual bleeding, endometriosis, and uterine fibroids. Findings can inform clinical practice and policy decisions to ensure that women have access to safe and effective contraceptive options that promote both reproductive and non-reproductive health.

ARTICLE HISTORY
Received 5 February 2024
Revised 26 May 2024
Accepted 21 June 2024

KEYWORDS
Menstrual health; hormonal contraceptives; uterine bleeding; endometriosis; uterine fibroids; and premenstrual dysphoric disorders

Background

The use of contraception is rising globally, with the number of users having increased from 663 million to 851 million over the last two decades. By the year 2030, it is projected that an additional 70 million women will be using contraceptives [1]. Of the 1.9 billion women of reproductive age (15-49 years), 1.1 billion report the need for contraceptives, which includes access to sexual and reproductive healthcare services and education, yet only 842 million women report meeting those needs [2]. This is often attributed to misconceptions or negative perceptions surrounding contraception. In developing regions, an estimated 257 million women who desire contraceptives refrain from utilising contraceptive techniques for a range of reasons, such as limited access to information or services, as well as inadequate support from their partners or communities. In many countries, data on contraceptives are only available for women of reproductive age who are married or in a union, further highlighting these barriers to access.

The cost burden associated with hormonal contraceptives undeniably poses a significant barrier to access and

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/13625187.2024.2373143.

consistent utilisation, potentially impacting menstrual health outcomes adversely. Financial constraints may lead to irregular use, increasing the risk of unintended pregnancies and health complications. However, amidst these challenges, global initiatives stemming from the International Conference on Population and Development (ICPD) underscore a collective commitment to address these issues. Efforts to ensure free provision of contraceptives within national reproductive health policies signify progress towards equitable access. By addressing economic barriers and promoting reproductive health rights, these initiatives strive to create a future where individuals can make informed choices about their reproductive health, regardless of financial constraints.

Methods of contraception come in three forms: short-acting, long-acting, and one-time barriers. Short-acting contraceptives include the pill (151 million users), injectables (74 million users, patches, and vaginal rings (less than 15 million users). Long-acting contraceptives include intrauterine devices (159 million users), implants (23 million users), and female sterilisation (219 million users). One-time barrier contraceptives include sponges, diaphragms, cervical caps, spermicide, female condoms, and male condoms; the prevalence of use is low for all one-time barrier methods except for male condoms (189 million users).

There is growing evidence of the benefits of contraceptives beyond pregnancy prevention. Within the United States, it is estimated that 1.5 million women take contraceptive pills for reasons other than pregnancy prevention, which has essential indications for women worldwide [3]. Evidence suggests that hormonal contraception may be effective in treating menstrual-related symptoms and disorders such as menorrhagia, dysmenorrhoea, and menstrual morbidity.

Hormonal contraceptive methods can impact a person's menstrual cycle, but the mechanism by which they do so varies. Combined oral contraceptive (COC) pills, for example, can provide control of the menstrual cycle by thinning the endometrium, thereby reducing menstrual blood loss. Because of this mechanism of action, COCs are often used to treat menorrhagia, a condition that results in excessive blood loss and can significantly impair a person's quality of life. On the other hand, the levonorgestrel intrauterine system (LNG-IUS) releases levonorgestrel so that a local foreign body reaction characterised by an increase in inflammatory cells is instigated, creating an unfavourable environment for implantation (Polis et al. 2018) as well as mucosal changes of the cervix. After insertion of the intrauterine device (IUD), many women experience a thinning of the endometrium, which lessens the amount of lining to be shed during the menstrual cycle, resulting in diminished menstrual bleeding. Individuals who menstruate often utilise contraceptives to suppress menstrual-related symptoms. In this way, contraceptives offer women control over the timing and number of pregnancies, but also in the management of medical and comfort concerns surrounding menstruation. Progestin-only contraceptive injectables and implants are highly effective, longer-acting contraceptive methods that most women can use in most circumstances.

Individuals who menstruate, health care providers, and program managers must be well-informed about the benefits and risks of each contraception method so that patients can receive high-quality health care. Legislators must also understand the health benefits of contraception to create policies that provide access to contraceptive resources. This study aims to identify and evaluate evidence that focuses on the use of contraceptives and their impact on menstrual morbidity outcomes among women of reproductive age. This review examines the association between the use of hormonal contraceptives and dysmenorrhoea, endometriosis, anaemia, menstrual irregularities, uterine fibroids, and amenorrhoea.

Methods

This systematic review is registered on Prospero (CRD42022332647) and relies on quantitative evidence regarding the use of contraceptives and their impact on non-reproductive outcomes among women of reproductive age. As for the **population**, we included women of reproductive age (14-49 years of age) presenting to primary healthcare clinics. If the studies were **interventional**, we included all contraceptive methods that the World Health Organisation (WHO) defines as effective and acceptable. Moreover, we included all therapeutic contraceptives that have been introduced earlier in therapeutic guidelines, such as mifepristone or medroxyprogesterone acetate pills. These are inclusive of 1) short-acting hormonal contraception (e.g. contraceptive pills, patches, and vaginal rings), 2) long-term contraception (e.g. hormonal intrauterine devices, implants, and injections), 3) one-time barrier contraception (e.g. condoms, sponges, diaphragms, cervical caps, and spermicide), 4) permanent contraception (e.g. tubal ligation and vasectomy), and 5) emergency contraception (e.g. morning after pill or IUD). If the studies were observational, contraceptives of all types (as stated above) were considered the main exposure. Any study which mixed contraception with other medications or modalities was excluded. The **comparison** was considered non-users or placebos. The **outcomes** of interest included menstrual-related morbidity (e.g. dysmenorrhoea, endometriosis, anaemia, menstrual irregularities, and amenorrhoea). We included studies with the following study designs: parallel or cluster randomised controlled trials, controlled clinical trials, controlled before and after studies, interrupted time series studies, cohort or longitudinal analyses, regression discontinuity designs, and case-control studies. The result of this systematic review is focused on hormonal contraceptives.

Data sources

To counteract the potential for publication bias, a comprehensive search for both published and unpublished studies was conducted from the date of inception until February 2022, with no restrictions on language or geographical location. We ran an updated search till October 2023, and no new related articles that matched our inclusion criteria were found under the title and abstract screening. A variety of databases were consulted, including CINAHL (1981-), OVID Medline (1946-), Embase (1947-), PsycINFO (1800s-), Maternity & Infant Care (1857-), LILACS (1982-), Clinicaltrials.gov (2000-), Web of science (1900-), Scopus (2004-), CENTRAL Database (1996-), and 13 local databases (further details of which can be found in Appendix I).

The search strategy was initiated with a Medline search utilising Medical Subject Headings (MeSH) terms and keywords, as Appendix II outlined independently or in combination. The search strategy was then adapted for the other databases consulted, including CINAHL, OVID Medline, Embase, PsycINFO, POLLINE, Web of Science, CENTRAL Database, Science Citation Index Expanded (SCIEXPANDED), and WHOLIS. In addition, reference lists of full-text papers relevant to the review were searched.

To augment the database search, OpenGrey (www.opengrey.eu), Google, and Google Scholar were utilised to search for relevant grey literature, and the websites of relevant societies and institutions devoted to contraception were consulted (see Appendix I).

We did not implement any language barrier. Studies that were systematic reviews, scoping reviews, narrative reviews, or meta-analyses were excluded from the review, along with a thesis, conference proceedings, commentaries, editorials, news, or protocol-only manuscripts. The search method was inclusive of all contraceptive methods, although the focus was hormonal contraceptives.

The retrieved articles were processed using Mendeley to remove duplicates and exported to Covidence software (Veritas Health Innovation, Melbourne, Australia) for title and abstract screening using eligibility criteria. The full texts of the included studies were then screened for quality appraisal and data extraction. To ensure that the review adequately addressed the main objectives of the study, the team analysed the inclusion criteria and summarised the characteristics of the included studies. The reasons for exclusion at the full-text screening stage were documented in the PRISMA flow diagram and reported in the findings section. Any discrepancies in the evaluation of studies were identified by Covidence and resolved through discussion.

The review team consisted of ten reviewers (SJ, OM, JM, JM, CC, MS, JA, CH, BJ, KC, AO) who screened the papers in pairs and achieved a Kappa score of more than 7. The screening process was managed by SJ, and conflicts were resolved through discussion. The Kappa score was obtained by reviewing ten abstracts at the abstract screening stage and ten full papers at the full-text screening stage. The abstracts were screened independently by two reviewers, each using Covidence. Full papers were divided among the reviewers for data extraction. One reviewer extracted the data, while another checked the extraction. The second reviewer was also responsible for creating forest plots in Revman. The same reviewers were responsible for completing the table of included studies, but there was not sufficient time to request clarifications or additional data from the researchers. Data collection was performed using data extraction forms stored securely on Google Drive and shared among all researchers. Summary tables were then created manually, and data were entered into Revman for analysis.

The studies were categorised into three primary types: randomised controlled trials (RCTs), cohort studies, and case-control studies. A forest plot was generated when two or more studies were available for comparison and outcome. When only a single study was available for a given outcome, a concise summary of the study was produced (see Appendix III) [4–20].

Analysis

We analysed individual women as the unit of analysis, focusing on methods used in original trial reports like intent-to-treat or per-protocol. It compared hormonal contraceptives versus no contraceptive or oral contraceptives versus no use, with subgroup analysis for different contraceptive types. Meta-analysis was conducted when studies compared identical methods, dosages, and regimens, using effect measures like odds ratios, risk ratios, mean differences, or standardised mean differences with 95% confidence intervals. These methods were chosen to ensure valid interpretation, facilitate data pooling, and communicate findings effectively. Despite intending to create forest plots at multiple time points, the follow-up period was shorter than clinically meaningful durations, and only the first and last reference periods were reported for outcomes. Attributes of included studies were recorded in a table, including author, publication year, country, aims, population, contraceptive type, dosage, outcome measures, and effect measures.

Subgroup analysis and sensitivity analysis

In the present study, subgroup analysis was performed to examine the impact of various types of contraception, dosage, and modes of administration on the outcomes, where feasible. Furthermore, sensitivity analysis was carried out to evaluate the robustness of the results by testing their dependence on the study quality. This was accomplished by systematically excluding each study from the analysis. Additionally, a sensitivity analysis was performed to assess the effect of loss to follow-up rates on the results by excluding studies with follow-up loss rates greater than 20%.

Assessment of heterogeneity

In the meta-analysis, we included only those comparisons and outcomes for which we had two or more data points. To assess heterogeneity, we evaluated the differences in study design, target population, and primary outcome measures among the included studies. Fixed and random-effect models were employed to evaluate the homogeneity of trials combined in the meta-analysis. The extent of heterogeneity was measured by Cochrane's Q, which was calculated as a weighted sum of the squared differences between individual study effects and the pooled effect across studies. The alpha level was set at 0.10, recognising that the chi-square test for heterogeneity is a low-power test. The magnitude of heterogeneity was then assessed using the I^2 score, and any score above 50% was investigated for the clinical and methodological diversity of the studies. In combining the data, we excluded studies that used different contraceptive methods, different doses of the same method, or different criteria for defining morbidity.

Due to limited time and resources, we could not contact authors or consult trial protocols for additional information on missing outcomes. Less than 20% of the data were missing. However, we consulted ClinicalTrials.gov to identify the trial protocols and determine the missing outcomes, and we compiled a list of authors for potential future correspondence to obtain the missing information.

Patient and public involvement

No patients were involved in this research. It is a systematic review, so the patients' priorities, experiences, and preferences did not inform the development of research questions and outcome measures. Patients were not involved in the design of the research. Further, this is not clinical research or randomised clinical trials.

Results

The Prisma chart in Figure 1 demonstrates the number of studies included in the search from different sources and the number of studies screened and included in the review.

A search was done for outcomes related to menstrual morbidity. A total of 44 studies were included in the analysis.

The total number of included studies was 44, 35 of which were randomised clinical trials (RCTs), one quasi-experimental, and eight observational studies (3 prospective, three retrospective, and two population-based). Table 1 shows some of the characteristics of RCTs, including country of origin, year of publication, number of facilities, type of health facility, level of health facility, sample size, study design, population, type of contraception studied, the outcome of interest extracted, and quality of study based on study design. Similar data (with exposure instead of intervention) was extracted for observational studies (Table 2). Most studies were from 2000 onward, while a handful were published before 2000 ($n=3$).

Women of reproductive health age between 14 and 49 were included. Some studies, however, noted the population as healthy women, while others noted women with particular conditions. For example, 14 studies focused on women with primary or secondary dysmenorrhoea, while 19 focused on endometriosis, eight on uterine fibroids, and five on abnormal or heavy bleeding.

Studies focused on either one type of contraception (e.g. oral contraception, ring/patch, implant, injection, IUD, condoms, sterilisation), a combination of contraceptives, or all hormonal contraceptives.

Outcomes of interest were menstrual health (e.g. endometriosis reoccurrence, uterine fibroids size reduction, heavy menstrual bleeding, and pain). The irregular menstruation outcome was presented in various forms. For instance, we extracted data on menstrual bleeding in the form of the level of haemoglobin (g/l) and pictorial blood loss assessment score. Amenorrhoea by 12 weeks was also collected,

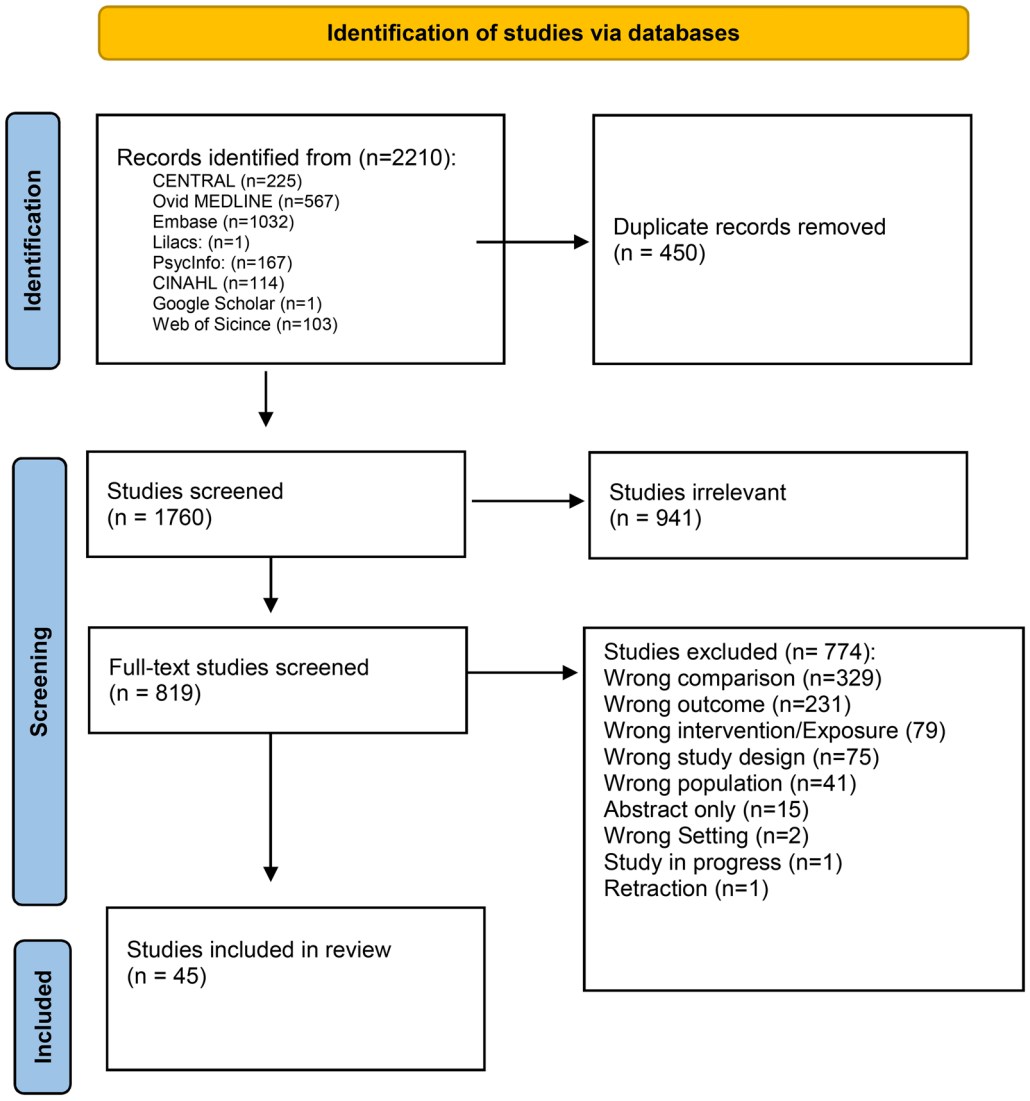

Figure 1. PRISMA flow diagram.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 1. Characteristics of RCTs.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Bagaria 2009	India	Teaching Hospital	RCT	40	Determine effectiveness of low-dose mifepristone in the treatment of uterine leiomyoma	Premenopausal women with symptomatic uterine leimyoma	Leiomyoma related symptoms, and uterine/leiomyoma volume	10 mg mifepristone (group 1) or placebo (group 2) daily for three months orally	3 months	Mifepristone caused significant improvement in leiomyoma-related symptoms. MBL declined by 94.8% in group 1 as compared to none in the placebo group at the end of therapy. MBL index as determined by the PBAC had certain limitations.	
Barati 2015	Iran	Hospital of Ahvaz from Feb 2010 to 2011	RCT	50	To compare polyp size before and after treatment	50 women aged 20-40 years with asymptomatic endometrial polyps smaller than 25 cm were randomised	Polyp size before and after treatment measured by US	Birth control pills of LD type were combination of 0.15 mg levonorgestrel and 0.03 mg ethinyl oestradiol	3 months	24% of the patients in the intervention group responded well to treatment, 32% reduction in size and 44% no change in polyps was observed. In control group, 28% size reduction, 37% with no change in size and 35% increase in size was observed. Size of polyps in the case group before and after treatment was significantly different (9.5 vs. 6.3 mm, $p<0.05$). However, the size of polyps before and after the study in the control group was not significant (9.5 vs. 8.6 mm, $p=0.297$).	
Barlow 2014	Europe and India	Multicentre	RCT	237	Invidualized bleeding experience of women with fibroids and anaemia using UPA	Women 18-50 years old, with uterine fibroids who were judged to have a sufficient problem to justify hysterectomy or myomectomy, and could participate in the study for 3 months leading up to surgery	Menstrual blood loss using PBAC tool, # of menstrual items used/ soiled, heavy menstrual bleeding	Participants receive ($n=96$ allocated, 95 receive) 5 mg UPA, or 10 mg UPA ($n=98$), or placebo ($n=48$) daily orally	3 months	Overall 63.1% of the UPA 5 mg group and 71.3% of the UPA 10 mg group had amenorrhoea or only very minimal spotting amounting to less than a total PBAC of,12 for the whole treatment phase. The other patterns of bleeding were less common: 'infrequent bleeding' (17.9% UPA 5 mg; 12.8% UPA 10 mg); 'frequent' or 'prolonged' bleeding or both (12.7% UPA 5 mg; 11.7% UPA 10 mg) and 'irregular' bleeding (5.3% UPA 5 mg; 3.2% 10 mg)	The impact of the UPA was that none of the women maintained regular periods and a majority had rapid relief from their excessive menstruation by entering amenorrhoea with the ending of the period

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Capmas 2021	France	Five teaching hospitals from June 16th 2016 to February 2nd 2018	RCT	40	To evaluate the effect of a 10 mg per day 12 week treatment of ulipristal acetate (UPA) on abnormal uterine bleeding due to adenomyosis.	Premenopausal women with abnormal uterine bleeding (with a pictorial blood loss assessment score (PBAC) higher than 100 at inclusion) and a sonographic or MRI diagnosis of adenomyosis.	The rate of women with a PBAC score of less than 75 during the 28 days following a 12-week treatment, rate of amenorrhoea at different times (5 weeks, 9 weeks, 13 weeks and 6 months) of the study, evolution of bleeding, anaemia, pain and analgesic consumption, evolution of quality of life, evolution of imaging (sonography or MRI) and treatment tolerance.	UPA 10 mg administered orally once a day for a 12 week period.	6 months	No woman in the placebo group versus 95.24 % of women in the UPA group had a PBAC score under 75 during the 28 day period following the 12-week treatment ($p < 0.01$). A significant decrease in pain was noticed between inclusion and 13 weeks in the UPA group ($p < 0.01$). At 6 months, there was no significant difference in PBAC score or pain between groups.	
Carbonell 2016	Cuba	University hospital 'Eusebio Hernández" Hospital, Havana, Cuba	Randomised controlled trial	360	To evaluate the effectiveness and safety of 2.5, 5 and 10 mg doses of mifepristone against a placebo in women with laparoscopic diagnostic of endometriosis.	Women with laparoscopic confirmed endometriosis who volunteered to take part in the study. Inclusion criteria: a) age 18 to 45, b) patients with dysmenorrhoea or pelvic pain not attributable to other gynecological illness and c) acceptance of using barrier contraceptive methods during treatment	prevalence of dysmenorrhoea and the average reduction in its intensity. Other variables used were: a) changes in AFS scores, b) changes in AFS stages, c) changes in the dimensions of the endometriotic lesions detectable by ultrasound and d) change in prevalence and intensity of symptoms of endometriosis. The intensity of each symptom was evaluated by means of a visual scale from 0 to 10.	Group I: 2.5 mg mifepristone per day for 6 months; Group II: 5 mg mifepristone per day for 6 months; Group III: 10 mg mifepristone per day for 6 months; and Group IV: a mifepristone placebo daily for 3 months were followed.	6 or 3 months	In the mifepristone groups, the prevalence of symptoms was significantly inferior to those at the beginning of treatment with no significant differences between the groups of 5 and 10 mg, unlike in 2.5 mg of mifepristone and the placebo group. The scores of the American Fertility Society were significantly different at the end of the treatment in the mifepristone groups. In the mifepristone groups, there were 9/264 (3.4%) subjects with raised hepatic transaminases up to 99 IU.	Authors concluded that the three mifepristone treatment groups display a noticeable therapeutic superiority over the placebo group. The 5 and 10 mg doses present a similar therapeutic efficacy but the 5 mg group has less side effects. The 2.5 mg group presents significantly lower percentages of amenorrhoea and clinical improvement than the 5 and 10 mg groups.
Carbonell Esteve 2012	Nicaragua	Eusebio Hernández Hospital, Havana, Cuba and the Alemán Hospital, Managua, Nicaragua.	Multicentre randomised clinical trial.	146	To evaluate the efficacy and safety of 2.5 mg and 5 mg mifepristone during 3 months for the treatment of uterine fibroids before surgery	Women with symptomatic uterine fibroids	Increase in average haemoglobin, changes in fibroid and uterine volume, and symptomatic improvement.	Group I: half a tablet of 5 mg (2.5 mg) mifepristone taken orally every 24 h, and Group II: one tablet of 5 mg mifepristone taken orally every 24 h over a period of 3 months in both groups. Two endometrial biopsies were performed.	3 months	The average haemoglobin at the end of treatment was 0.6 g/dL greater in the 5 mg mifepristone group ($p = 0.033$). In both groups there were similar reductions in fibroid volumes.	

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Catherino 2017	United States	25 study centres across the United States	RCT	157	To assess efficacy and tolerability of ulipristal acetate, a selective progesterone receptor modulator, for treatment of symptomatic uterine leiomyomas.	Premenopausal women (aged 18–50 years) with abnormal uterine bleeding, one or more discrete leiomyomas, and uterine size 20 weeks of gestation or less	Coprimary endpoints were rate of and time to amenorrhoea, defined as no bleeding for the last 35 consecutive days of treatment. Secondary endpoints included rates of amenorrhoea from day 11 and change from baseline to endpoint in the Revised Activities subscale of the Uterine Fibroid Symptom and Quality of Life questionnaire.	5 mg ulipristal, 10 mg ulipristal, or placebo once daily for 12 weeks	24 weeks	Amenorrhoea was achieved by 25 of 53 (47.2% [97.5% CI 31.6–63.2]) and 28 of 48 (58.3% [97.5% CI 41.2–74.1]) patients treated with 5 mg and 10 mg ulipristal, respectively, compared with 1 of 56 (1.8% [97.5% CI 0.0–10.9]) placebo-treated patients (both $p<.001$). Time to amenorrhoea was shorter for both ulipristal doses compared with placebo ($p<.001$), and both doses of ulipristal resulted in improved quality of life compared with placebo ($p<.001$).	
Chen 2017	China	The participants were recruited from a tertiary medical centre in Northern Taiwan	Randomised controlled trial	80	To evaluate whether a maintenance l evonorgestrel-releasing intrauterine system is effective for preventing postoperative endometrioma recurrence	Women with dysmenorrhoea and a sonographic diagnosis of endometrioma who were scheduled for elective laparoscopic ovarian cystectomy surgery were included in the study.The inclusion criterion was moderate and severe symptomatic endometriosis (stages 3 and 4) according to the revised American Society for Reproductive Medicine (ASRM) classification, with a chocolate-containing cyst observed during laparoscopic surgery	The primary outcome was endometrioma recurrence assessed withsonography 1, 3, 6, 12, 15, 18, 21, 24, 27, and 30 months after treatment. The secondary outcomes were the severity of the dysmenorrhoea, the CA125 level, noncyclic pelvic pain, and side effects 30 months after surgery. Dysmenorrhoea and noncyclic pelvic pain were measured using a linear visual analog scale (VAS)	levonorgestrel-releasing intrauterine system or expectant management during 30 months	30 months	Endometrioma recurrence at 30 months did not significantly differ between the 2 groups (the intervention group, 10 of 40, 25% vs the control group 15 of 40, 37.5%; hazard ratio, 0.60, 95% confidence interval, 0.27-1.33, $p = .209$). The intervention group exhibited a lower dysmenorrhoea recurrence rate, with an estimated hazard ratio of 0.32 (95% confidence interval, 0.12-0.83, $p = .019$). Over a 30 month followup, the intervention group exhibited a greater reduction in dysmenorrhoea as assessed with a visual analog scale score (mean SD, 60.8 25.5 vs 38.7 25.9, $p < .001$, 95% confidence interval, 10.7-33.5), noncyclic pelvic pain visual analog scale score (39.1 10.9 vs 30.1 14.7, $p = .014$, 95% confidence interval, 1.9−16.1), and CA125 (median [interquartile range], −32.1 [-59.1 to 14.9], vs −15.6 [-33.0 to 5.0], $p = .001$) compared with the control group. The number-needed-to-treat benefit for dysmenorrhoea recurrence at 30 months was 5.	Authors concluded that long-term maintenance therapy using a levonorgestrel-releasing intrauterine system is not effective for preventing endometrioma recurrence

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Cucinella 2013	Italy	Three university hospitals d between September 2009 and August 2010.	Quasi-experimental study	168	To analyse the endometrioma recurrence rate in patients who underwent laparoscopic excision followed by postoperative longterm regimen of oral contraceptives (OCs).	Females 18 to 40 years who were not attempting to conceive.	Rate of recurrent endometria	Group A: no COC Group B: monophasic pill with EE 20 lg and 0.15 mg desogestrel daily Group C: monophasic pill with EE 20 lg and gestodene 0.075 mg daily; Group D: multiphasic pill with 2 mg E2V for 22 days, with 2 mgdienogest for the first 5 days and 3 mg on the remaining17 days, the other four: pill with only E2V and two: placebo pill	24 months	The rate of endometrioma recurrence was statistically significant in the COC non-users compared with Group B (RR 4.85; 95 % CI 1.77–13.28), Group C (RR 5.73; 95 % CI 2.04–16.09) and Group D (RR 9.16; 95 % CI 3.05–27.53), respectively.	Authors concluded that long-term OC use after conservative surgery can be useful for the prevention of ovarian endometrioma recurrence.
Davis 2000	United States	Multicentre study	Randomised Clinical Trial	201	To compare the efficacy of a triphasic combination oral contraceptive (OC) containing norgestimate and ethinyl oestradiol (E2) and placebo in the treatment of metrorrhagic, menometrorrhagic, oligomenorrheic, and polymenorrheic dysfunctional uterine bleeding (DUB).	All eligible subjects provided informed consent, were between 15 and 50 years of age; in good general health, not pregnant or nursing, and had at least a 2-month history of metrorrhagic, menometrorrhagic, oligomenorrheic, or polymenorrheic DUB that was not attributable to systemic disease or structural pathology.	The primary efficacy variables were the investigator's overall assessment score of the resolution of the subject's DUB (excellent, good, fair, no change, worse, unable to evaluate) and the subject's self-assessment score (much improved, improved, slightly improved, no change, worse, don't know). The secondary efficacy variables included abnormal uterine bleeding patterns during the 84-day reference period and an evaluation of the change from baseline in quality-of-life scores at the final visit. The 84-day reference period analysis included an evaluation of the presence or absence of abnormal bleeding patterns and, more specifically, the frequency	For each of the three 28-day treatment cycles, subjects assigned to treatment received the following daily doses: days 1–7, 0.180 mg norgestimate/0.035 mg ethinyl E2; days 8–14, 0.215 mg norgestimate/0.035 mg ethinyl E2; days 15–21, 0.250 mg norgestimate/0.035 mg ethinyl E2; and days 22–28, inactive tablets. Subjects randomised to placebo treatment received identical placebo tablets.	84days (3 oral contraceptives cycles)	More than 80% of subjects receiving triphasic norgestimate-ethinyl E2 had improvements in their abnormal bleeding patterns as assessed by investigators, and the subjects themselves compared with fewer than 50% of subjects in the placebo treatment group ($p < .001$). Abnormal bleeding patterns were reported by significantly fewer subjects receiving triphasic norgestimate-ethinyl E2 than in the placebo treatment group ($p < .001$). Change from baseline in physical functioning (e.g. self-care, walking, lifting, exercising) was significantly more improved in the triphasic norgestimate-ethinyl E2 group than in the placebo group	Authors suggest that the triphasic combination of norgestimate and ethinyl E2 is an effective treatment for metrorrhagic, menometrorrhagic, oligomenorrheic, and polymenorrheic dysfunctional uterine bleeding.

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Donnez 2012	UK, Belgium, Hungary, Switzerland, France and Russia	Multicentre study	Randomised Clinical Trial	242	To determine the effects of 5 mg of ulipristal acetate per day and 10 mg of ulipristal acetate per day on uterine bleeding and fibroid volume in women with symptomatic fibroids who were planning to undergo surgery	Women 18 to 50 years of age were eligible if they met the following criteria: a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation, fibroidrelated anaemia, defined as a haemoglobin level of 10.2 g per decilitre or ower without macrocytosis; a myomatous uterus with a size equivalent to that of a uterus at 16 weeks or less of gestation; at least one fibroid that was 3 cm or more in diameter, but with no fibroid measuring more than 10 cm in diameter, as measured by ultrasonography; and a body-mass index (the weight in kilograms divided by the square of the height in metres) of 18 o 40	The coprimary efficacy end points were the percentage of patients with a reduction in uterine bleeding at week 13, defined as a PBAC score (summed over the preceding 28-day period) of less than 75, and the change in total fibroid volume from screening to week 13, as assessed by magnetic resonance imaging (MRI) and read centrallyby a radiologist who was unaware of the studygroup assignments. The total fibroid volume was the sum of the individual fibroid volumes.	Patients were randomly assigned, in a 2:2:1 ratio, to receive 5 mg of ulipristal acetate per day, 10 mg of ulipristal acetate per day, or placebo (one pill per day, provided by PregLem)	13 weeks	At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg of ulipristal acetate, 92% of those receiving 10 mg of ulipristal acetate, and 19% of those receiving placebo ($p < 0.001$ for the comparison of each dose of ulipristal acetate with placebo). The rates of amenorrhoea were 73%, 82%, and 6%, respectively, with amenorrhoea occurring within 10 days in the majority of patients receiving ulipristal acetate. The median changes in total fibroid volume were −21%, −12%, and +3% ($p = 0.002$ for the comparison of 5 mg of ulipristal acetate with placebo, and $p = 0.006$ for the comparison of 10 mg of ulipristal acetate with placebo).	Authors concluded that treatment with ulipristal acetate for 13 weeks effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids.
Engman 2009	Sweden	Teaching hospital	Prospective, randomised, placebo-controlled study	30	To evaluate the effect of 3 months of mifepristone treatment on leiomyoma volume, endometrium and bleeding.	Females who were healthy, nonpregnant, and referred for evaluation to the outpatient clinic due to leiomyoma related problems indicating surgical intervention.	Reduction in uterine leiomyoma size was the primary outcome.	Mifepristone, 50 mg daily for 3 months.	3 months	In the treatment group, total leiomyoma volume was −28 (-48, −8)% compared to 6 (-13, 25) % in the placebo group. This was a statistically significant difference ($p = 0.021$).	Authors concluded mifepristone may be an effective treatment for uterine leiomyoma.
Esteve 2013	Cuba	Teaching hospital	Randomised, double-blind clinical study	124	To evaluate the efficacy, safety, and quality of life of 5 mg mifepristone per day compared with a placebo in treating uterine fibroids.	Females 18 years or older with uterine fibroids.	Changes in fibroid and uterine volumes, changes in symptom prevalence and intensity, and changes in quality of life.	Mifepristone, 5 mg daily for 3 months.	3 months	After three months of treatment, fibroid volume was reduced by 28.5% in the mifepristone group compared to an increase of 1.8% in the placebo group ($p = 0.031$). Pelvic pain prevalence ($p = 0.006$), pelvic pressure ($p = 0.027$), rectal pain ($p = 0.013$), hypermenorrhea ($p = 0.001$), and metrorrhagia ($p = 0.002$) were significantly different between the groups at the end of treatment.	Authors concluded that mifepristone (5 mg) was significantly more effective than the placebo.

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Fiscella 2006	United States	Baseline physical and biochemical examinations were performed in a hospital setting.	Randomised controlled trial	42	To assess the effect of low-dose mifepristone on quality of life, pain, bleeding, and uterine size among women with symptomatic leiomyomata.	Females 18 years or older who were premenopausal, reported more than 39 on the Uterine Fibroid Symptom Quality of Life Symptom Severity Subscale, had a total uterine volume of 160 mL or more by vaginal and abdominal ultrasound, and at least one leiomyoma of 2.5 cm or greater.	Leiomyoma-specific quality of life was the primary outcome. Presence of leiomyoma symptoms and drug adverse effects, uterine volume, leiomyoma size and number were also assessed.	Mifepristone, 5 mg daily for 26 weeks.	6 months	Compared with the placebo group, women who received the intervention had improved leiomyomaspecific quality of life, 41% became amenorrheic, rates of anaemia improved, and adjusted uterine size was reduced by 47% ($p<.05$ to .001).	Authors concluded that low-dose mifepristone reduced leiomyoma size and improved leiomyoma-specific quality of life among the study population.
Fox 2019	EU, Australia, New Zealand, South America, Mexico and South Africa	38 study sites	Randomised Clinical Trial	439	To evaluate the effect of investigational vaginal rings containing nomegestrol acetate (NOMAC) plus 17β- oestradiol (E2) or etonogestrel (ENG) plus E2 in women with moderate to severe primary dysmenorrhoea	Otherwise healthy women 18 to 50 years of age with regular menstrual cycles (cycle length 23–35 days) who reported moderate to severe primary dysmenorrhoea.	The primary endpoint was the change from baseline to Cycle 2 in mean menstrual pain score (mean of three highest pain scores during the cramping window). Secondary endpoints included change from baseline versus placebo to Cycle 2 in mean total impact score, number of ibuprofen tablets used for menstrual pain, and number of days of ibuprofen intake. Additionally, the responder rate per cycle was determined; a responder was defined as a participant with at least a 1-point reduction in pain score, as compared to baseline.	This was a randomised, placebo-controlled, multicentre, double-blind study with five groups: NOMAC-E2 700/300, NOMAC-E2 900/300, ENG-E2 100/300, ENG-E2 125/300 and placebo vaginal rings.	50 days	The mean pain score decreased from baseline to Cycle 2 in all groups; the decrease in all four treatment groups compared to placebo was statistically significant (p-values <= 0.002). All treatment groups had greater reductions than placebo in ibuprofen intake and greater improvement in impact scores; these differences were statistically significant for both endpoints for the ENG-E2 100/300 µg/day group, while the other groups were not statistically significant for one or both endpoints	The authors concluded that all four investigational rings produced a statistically significantly larger reduction from baseline in mean menstrual pain score compared to placebo while pain medication use decreased.

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Fraser 2011	Europe and Australia	34 centres in Europe and Australia	Randomised, double-blind, placebo-controlled Phase III trial	231	To investigate the efficacy and safety of oestradiol valerate/dienogest (E2V/DNG) for the treatment of heavy menstrual bleeding without recognisable organic pathology.	Healthy women with idiopathic heavy, prolonged or frequent menstrual bleeding	MBL volume, number of sanitary items used, and iron metabolism parameters, adverse events (anaemia, anxiety, dysmenorrhoea, headache, etc.)	E2V/DNG was orally administered using an oestrogen step-down and progestogen step-up approach (E2V 3 mg on Days 1 – 2, E2V 2 mg/DNG 2 mg on Days 3 – 7, E2V 2 mg/ DNG 3 mg on Days 8 – 24, E2V 1 mg on Days 25 – 26 and placebo on Days 27 – 28; E2V 1 mg = E2 0.76 mg). Study medication was initiated on the first day of bleeding after randomisation, and there were no tablet-free days between treatment cycles.	344 days	This pooled analysis shows that E 2V/DNG rapidly reduces MBL in women with heavy and/or prolonged menstrual bleeding. After six months of treatment, i.e. by treatment cycle 7, the median MBL was reduced by 88% in the intervention group vs 24% in the placebo group.	Medications containing iron was reported in 45 of 269 women (16.7%) in the E 2V/DNG group and in 39 of 152 women (25.7%) in the placebo group.
Harada 2008	Japan	18 Clinical trial sites (13 clinics, 5 hospitals)	Double-blind, randomised, placebo-controlled trial	100	To evaluate the efficacy of a low-dose oral contraceptive pill (OCP) for patients with dysmenorrhoea associated with endometriosis.	Patients with dysmenorrhoea associated with endometriosis	A zero- to three-point verbal rating scale and a visual analogue scale to measure the severity of disability because of dysmenorrhoea in daily life, and the patients' use of analgesics.	Monophasic OCP (0.035 mg plus norethisterone 1 mg) for 21 days, plus 7 days of placebo for 4 cycles	6 cycles	The reduction in pain score was significantly higher in the OCP group (2.0) compared with the placebo group (0.6) (p<.0001).	
Harada 2011	Japan	Clinical trial sites in Japan	Placebo-controlled, double-blind, randomised trial.	115	To evaluate the efficacy and safety of low-dose oral contraceptives (IKH-01; 0.035 mg ethinyl oestradiol and 1 mg norethisterone) for patients with primary dysmenorrhoea.	Patients with primary dysmenorrhoea	Total dysmenorrhoea score, verbal rating scale defining pain according to limited ability to work and need for analgesics, and visual analog scale (VAS).	Patients randomly assigned to receive IKH-01 (0.035 mg ethinyl oestradiol and 1 mg norethisterone orally) or placebo for four cycles.	5 cycles	The reduction in total dysmenorrhoea score was significantly higher in the IKH-01 group (-2.6) compared with the placebo group (-1.4) (p<.001). The reduction in VAS was significantly higher in the IKH-01 group (-36.0) compared with the placebo group (-20.8; p = .001).	

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Harada 2016	Japan	18 Clinical trial sites	Placebo-controlled, double-blind, randomised trial.	215	To evaluate the efficacy and safety of an ultra-low-dose oral contraceptive (NPC-01; 0.02 mg ethinyl oestradiol and 1 mg norethisterone) in subjects with dysmenorrhoea.	Women with dysmenorrhoea	Total dysmenorrhoea score (verbal rating scale) assessing pain on the basis of limited ability to work and need for analgesics.	The subjects with primary dysmenorrhoea were randomised at a ratio of 2:1 to receive NPC-01 (0.02 mg EE and 1 mg NET) or placebo. The subjects with secondary dysmenorrhoea were randomised at a ratio of 2:1:2 to receive NPC-01, placebo, and IKH-01 (0.035 mg EE and 1 mg NET). The treatment was initiated on the third day (±2 days) of the menstrual cycle for 21 days, followed by 7 days free of any medication and continued for four cycles.	5 cycles	The reduction of total dysmenorrhoea score was significantly higher in the NPC-01 group (2.3) than in the placebo group (1.3) ($p<.001$). Similarly, the reduction of VAS score was significantly higher in the NPC-01 group (30.6) than in the placebo group (13.0) ($p<.001$).	
Harada 2017	Japan	Thirty-two centres in Japan	Randomised, double-blind, placebo-controlled, parallel-group study	312	To investigate the efficacy and safety of ethinylestradiol 20 ug/drospirenone 3mg n a flexible extended regimen (FlexibleMIB) compared with placebo to treat endometriosis-associated pelvic pain (EAPP).	Patients aged ≥20 years with a clinical diagnosis of endometriosis who had pelvic tenderness, induration in the cul de sac, or uterine immobility, as well as patients diagnosed as having endometriosis by laparotomy/ laparoscopy or by the identification of endometriomas.	Absolute change in the most severe EAPP based on visual analog scale scores from the baseline observation phase to the end of the double-blind treatment phase.	Patients randomised to FlexibleMIB received one tablet of ethinylestradiol 20 ug/ drospirenone 3 mg per day, and treatment began between the first and fifth day of menstruation. Tablets were administered continuously for 120 days, followed by a 4-day tablet-free interval. In the event of R3 consecutive days of spotting and/or bleeding on days 25–120 of the cycle, patients began and completed the 4-day tablet-free interval, then started the next cycle of treatment.	52 weeks	Compared with placebo, FlexibleMIB significantly reduced the most severe EAPP (mean difference in visual analog scale score: −26.3 mm, 95% confidence interval −31.6 to −20.9; $p<.0001$).	

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Harada 2021	Japan	18 private clinics across Japan	Placebo-controlled, double-blind, randomised trial	251	To evaluate the efficacy and safety of 28-day Cyclic and 84-day Extended regimens of NPC-16 (ethinylestradiol 0.02 mg plus levonorgestrel 0.09 mg) in patients with dysmenorrhoea.	Primary and secondary dysmenorrhoea patients	A comparison of the efficacy and safety of the Cyclic and Extended NPC-16 regimen for the treatment of dysmenorrhoea relative to the Placebo.	NPC-16-Cyclic regimen: NPC-16 for 21 days, followed by the placebo for 7 days (one cycle: 28 days) for 13 cycles. NPC-16-Extended regimen: NPC-16 for 77 days, followed by the placebo for 7 days for four cycles, followed by one cycle of the Cyclic regimen.	13 cycles	The reduction in total dysmenorrhoea score was significantly greater in both the Cyclic group (−1.8) and Extended group (−3.1) than in the Placebo group (−0.9; $p<.01$) among patients with dysmenorrhoea.	
Harrison 2000	Ireland	The Infertility Unit, Rotunda Hospital, Dublin, Ireland.	Prospective, randomised, double-blind, placebo-controlled trial.	100	To determine the efficacy of medroxyprogesterone acetate (MPA), 50 mg/d for 3 months, in treating endometriosis.	Infertile women found to have endometriosis at laparoscopy	Initial and second-look laparoscopy for revised American Fertility Society stages and scores, pregnancies achieved, effects on well-being *via* symptomatic improvement, and side effects.	Medroxyprogesterone acetate (MPA) tablets, 50 mg/d orally for 3 months	24 weeks	After therapy, second-look laparoscopy again showed no significant intergroup differences between the MPA and placebo groups in terms of stage or score ($p < .77$)	
Hendrix 2002	United States	Twenty-three clinics in the United States	Randomised, double-blind, placebo-controlled exploratory study	77	To assess the safety profile and the effect on symptoms of primary dysmenorrhoea of an OC that contains a low oestrogen dose and a shortened placebo period with an extended low unopposed ethinyl oestradiol dose to finish the cycle.	Women who were no older than 32 years of age and who had a documented history of primary dysmenorrhoea for at least four consecutive cycles	The intensity of menstrual-related distress was measured with the Menstrual Distress Questionnaire (MDQ).	21 days of 150 g DSG plus 20 g EE (white tablets), 2 days of placebo (green tablets), and 10 g EE for 5 days (yellow tablets) for four consecutive 28-day	112 days	Participants receiving DSG/EE&EE recorded reduced menstrual pain severity (mean difference −0.3, $p=0.074$), lower total MDQ scores (mean difference −7.5, $p=0.095$), and significantly less menstrual cramping (mean difference −1.1, $p<0.001$). No significant change in bloating, anxiety, loneliness, weight gain, or acne was reported.	
Irahara 2020	Japan	38 sites in Japan	Randomised, double-blind, placebo-controlled trial	121	To evaluate the efficacy, safety, and appropriate dose of ulipristal acetate (UPA) in Japanese women with symptomatic uterine fibroids (UFs)	Premenopausal women with uterine fibroids	The rate of patients having achieved amenorrhoea for 35 days at Week 12	Ulipristal acetate (UPA) 2.5 mg, UPA 5 mg, and UPA 10 mg were orally administered once a day for 12 weeks. 1.88 or 3.75 mg of leuprorelin acetate (LEU) was subcutaneously administered once every 4 weeks.	24 weeks	The rates for amenorrhoea were 4.5%, 60.0%, 72.7%, 88.0%, and 76.2% in the placebo, UPA-2.5 mg, UPA-5 mg, UPA-10 mg, and LEU groups, respectively.	

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Jensen 2011	United States and Canada	47 centres in the US and Canada between December 2005 and May 2008	Randomised, double-blind, placebo-controlled trial	190	To estimate the efficacy of a fixed oestrogen step-down and progestin step-up 28-day oestradiol (E2) valerate and dienogest oral contraceptive regimen in women with heavy menstrual bleeding, prolonged menstrual bleeding, or heavy and prolonged menstrual bleeding without organic pathology.	Women aged 18 years or older with prolonged, frequent, or heavy menstrual bleeding.	The primary outcome was the proportion of participants with a complete response to treatment (i.e. return to complete menstrual normality). Secondary efficacy variables included changes in menstrual blood loss volume; the number of sanitary protection items used; changes in the number of bleeding days and episodes; the proportion of participants cured of individual symptoms; and changes in iron metabolism parameters.	The intervention was dispensed in blister cards containing 28 tablets. The contents of the cards included E2 valerate 3 mg on days 1–2 (1 mg of E2 valerate is equivalent to 0.76 mg of E2), E2 valerate 2 mg and dienogest 2 mg on days 3–7, E2 valerate 2 mg and dienogest 3 mg on days 8–24, E2 valerate 1 mg on days 25–26, and placebo on days 27–28.	90 days	The proportion of participants with a complete response to treatment was significantly higher in the treatment group (35/80; 43.8%) compared with the placebo group (2/48, 4.2%, $p<.001$). The mean (SD) reduction in menstrual blood loss with the treatment from the run-in phase to the efficacy phase was substantial, 353 mL (309 mL), and significantly greater than that in placebo recipients, 130 mL (338 mL); significant improvements in haemoglobin, haematocrit, and ferritin were seen with E2 valerate and dienogest, but not with placebo.	Authors concluded oral E2 valerate and dienogest are highly effective in the treatment of women with heavy menstrual bleeding, prolonged menstrual bleeding, or heavy and prolonged menstrual bleeding without organic pathology.
Lang 2018	China	23 Chinese hospitals	Randomised controlled trial	255	The aims of this 24-week, double-blind, randomised placebo-controlled phase 3 study were to investigate the efficacy and safety of dienogest 2 mg once-daily treatment in Chinese women with endometriosis and to seek marketing authorisation in China	The study enrolled women aged 18–45 years with a diagnosis of endometriosis confirmed by laparoscopy or laparotomy within 10 years before study entry	Mean absolute change in endometriosis-associated pelvic pain from baseline to week 24, measured on a visual analog sclae covering an observation period of 4 weeks before the respective time point of assessment and at 4-weekly intervals.	Group I: Dienogest 2 mg once daily, Group II: Placebo	24 weeks	After 24 weeks of treatment, the difference between treatment arms for mean reduction in EAPP was statistically significant in favour of dienogest (-24.54 mm; 95% CI −29.93 to −19.15; $p < 0.0001$). Secondary efficacy analyses supported the significant superiority of dienogest over placebo. Dienogest was well tolerated, with few AEs associated with therapy. Dienogest had no effect on BMD levels after 24 weeks of treatment	Authors concluded that Dienogest 2 mg once daily for 24 weeks was superior to placebo in reducing EAPP and was safe and well tolerated in Chinese women with endometriosis. The results are consistent with studies previously conducted in European women

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Mehdizadeh Kashi 2022	Iran	Hazrat-e Rasoole-Akram hospitals affiliated to Iran University of Medical Sciences	Randomised controlled trial	108	To compare the effects of dienogest and a combined oral contraceptive pill (COCP) after laparoscopic surgery on pain and quality of life in women with severe endometriosis	Women with severe endometriosis confirmed by laparoscopic surgery who fulfilled the following inclusion criteria were enrolled in the study: (1) age 18–45 years; (2) body mass index (BMI, calculated as weight in kilograms divided by height in metres squared) 18.5– 29.9; (3) stage IV endometriosis according to the revised American Society for Reproductive Medicine classification15; (4) presence of subjective symptoms during menstruation (dysmenorrhoea, dyspareunia, dysuria, dyschezia, pelvic pain)	Changes in the patients' self-reported pain levels were defined as the primary outcome. To measure this criterion, scores for pelvic pain, dyspareunia, dysuria, and dyschezia were assessed and compared in the three groups. Pelvic pain and dyspareunia scores were measured on a 10-point visual analog scale. A three-point score was available for items concerning dysuria and dyschezia.	The first group received 2 mg dienogest (Visanne; Bayer AG, Berlin, Germany) daily for 6 months; the second group received a COCP containing 30 µg ethinylestradiol and 0.3 mg levonorgestrel (OCPs; Aburaihan Pharmaceutical Co) daily for 6 months; and the third group received a placebo	6 months	Treatment with dienogest or COCP was associated with improved selfreported pain after 6 months of treatment, as evidenced by significantly lower scores for pelvic pain and dyspareunia compared with placebo Significant differences in dyspareunia score were observed at 6 months in the dienogest, COCP, and placebo groups (mean difference −2.14, −2.86, and −0.48 respectively; $p = 0.040$.	Authors concluded that postoperative administration of dienogest or COCP reducedendometriosis-associated pain and improved quality of life in women with severe endometriosis.
Muzii 2000	Italy	Not reported	Randomised controlled trial	70	To evaluate the efficacy of postoperative administration of monophasic, combined, low-dose oral contraceptives on endometrioma recurrence and on persistence-recurrence of associated pain symptoms after laparoscopic treatment of moderate-to-severe endometriosis.	Patients who were not attempting to conceive, aged 20 to 35 years, that underwent laparoscopic excision of ovarian endometriomas, patients with ultrasonographic evidence of ovarian endometriomas were invited to enter this study, and they gave their informed consent. No patients were attempting to conceive at the time of study entry. In all patients either moderate-to-severe dysmenorrhoea or chronic pelvic pain, or both, was present (either symptom graded as ≥4 on a 10-point visual analog scale). Before surgery, all patients underwent at least 2 transvaginal ultrasonographic scans at least 8 weeks apart to confirm the presence of ovarian cysts with ultrasonographic features of endometriomas.	At 3 and 6 months after surgery, followed by 6-month intervals, both groups underwent clinical and ultrasonographic examination for possible evidence of endometrioma recurrence, and each patient was evaluated for the absence, persistence, or recurrence of pain symptoms. Pain recurrence was defined as severity of pain graded ≥4 on a 10-point visual analog scale. In case of an ultrasonographic scan suggesting evidence of endometrioma recurrence, the scan was repeated after 2 to 3 spontaneous cycles to confirm the diagnosis.	Cyclic monophasic combined oral contraceptives (ethinyl oestradiol, 0.030 mg, and gestodene, 0.075 mg, daily for 21 days followed by a 7-day interval) for 6 months or no further treatment.	6 months	Two patients in the oral contraceptive group did not complete the study. After a mean follow-up of 22 months (range, 12-48 months), there were 2 (6.1%) endometrioma recurrences in the 33 patients who received postoperative oral contraceptives versus 1 (2.9%) recurrence in the 35 patients in the control group (not significant). The moderate-to-severe pain recurrence rate was 9.1% in the oral contraceptive group versus 17.1% in the control group (not significant). The mean time to recurrence of either symptoms or endometriomas was 18.2 months in the oral contraceptive group versus 12.7 months in the control group. The 12-month cumulative recurrence rate at life-table analysis was significantly lower for patients receiving oral contraceptives versus control subjects, whereas no significant difference was evident at 24 and 36 months	Authors concluded that postoperative administration of low-dose cyclic oral contraceptives does not significantly affect the long-term recurrence rate of endometriosis after surgical treatment. A delay in recurrence is evident at life-table analysis

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Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Niakan 2021	Iran	Rasoul-e-Akram hospital, affiliated to Iran University of Medical Sciences, Tehran, Iran, between March 2018 and March 2020.	Randomised double-blind trial	90	To compare the effect of dienogest and oral contraceptive pills (OCPs) on pain and QOL in women with endometriosis.	Women women aged 18–45 years with a body mass index (BMI) 18.5–24.9 kg/m2 who have severe endometriosis confirmed by laparoscopic surgery.	The primary outcome was patient pain including dyspareunia, dysuria, dyschezia, and pelvic pain. The secondary outcome was change in patients' quality of life (QOL) score.	Participants were randomised to dienogest (Vissane 2 mg tablet; $n=30$), OCPs (LD; $n=30$), or placebo ($n=30$) daily for 12 weeks.	12 weeks	Pelvic pain was significantly reduced among the treatment groups, while the effect of medication on dysuria and dyschezia was not significant. The overall QOL score between the control and dienogest ($p=0.02$) and OCPs groups ($p=0.001$) was significantly different; however, the difference was not significant between the two intervention groups.	Authors concluded that there is no difference in the efficacy of dienogest and OCPs in management of pain and the QOL but that there was a significant difference between the placebo and intervention groups.
Osuga 2020	Japan	Twenty study sites	Randomised, double-blind, multicentre, placebo-controlled study	235	To evaluate the efficacy, safety, and clinically recommended dose of dienogest (DNG; 0.5 mg/d, 1 mg/d, and 2 mg/d) in the treatment of primary dysmenorrhoea.	Patients with primary dysmenorrhoea	The change from baseline in the dysmenorrhoea score at week 12 of treatment.	Patients were randomised to receive orally a placebo, DNG (0.5 mg/d, 1 mg/d, or 2 mg/d) or ethinylestradiol 0.02 mg/ drospirenone 3 mg (an open-label reference drug) for 12 weeks.	12 weeks	All DNG arms were superior to the placebo arm in terms of the change from baseline in the dysmenorrhoea score. In the comparison with the EE/ DRSP arm, the differences in the least square mean and its two-sided 95% confidence interval (lower limit, upper limit) were 0.9 (0.2, 1.5) in the placebo arm, −0.3 (-1.0, 0.4) in the DNG 0.5 mg/d arm, −0.8 (-1.4, −0.1) in the DNG 1 mg/d arm, and −1.2 (-1.8, −0.5) in the DNG 2 mg/d arm.	
Parsanezhad 2003	Iran	Shiraz University of Medical Sciences, Shiraz, Iran	Randomised Clinical Trial	1358	To evaluate the influence of five sterilisation techniques on both menstrual pain and indices, using both the pre-surgical menstrual status of the same women and a group of nonsterilized women as control	All women were selected from a low-income population. Those a least 25 and at most 40 years of age by the time of sterilisation, normal menstruation cycles with a mean length of 21 to 35 days, intra-individual variation of ±3 days (but never outside the 21 to 35 days range), and a good physical and mental health were included into the study	In each follow up session, every single change in the patient's menstrual indices was noted. The persistent change in the menstrual indices was defined as any change from the baseline that persisted for at least two postoperative follow up visits. Regarding the duration of bleeding, significant changes were categorised into either less than four days, between four and eight, and more than eight days. For the length of the menstrual cycle, significant changes were categorised into either less than 21 days, between 21 and 35, and more than 35 days persisted at least in two follow up visits	One of the five methods of tubal sterilisation; unipolar electrocauterization, bipolar electrocauterization, minilaparatomy, Pomeroy method, Falope ring, and Hulka clip	3 years	Menstrual indices were significantly different between the control group and those women who were sterilised by unipolar, ring, and Pomery methods. The amount of bleeding, was increased by 28.3% in unipolar group ($p=0.001$), 19.9% in ring group ($p=0.001$), and by 23.9% in Pomeroy group ($p=0.0001$). Significant menstrual pain lasted for a maximum of 18 months was noted in unipolar coagulation group ($p=0.0001$).	The authors concluded that sterilisation methods which destroy the vascular communications along and immediately subjacent to the tube and that also disturb the countercurrent exchange of biologically active factors between the uterus and ovaries, are more likely to cause menstrual abnormalities

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Petraglia 2009	Italy	Academic Health Centre of Siena	RCT	55	Effectivness of oral contraceptives at controlling fertility outcomes in women following myomectomy	Women aged 30-45, BMI 22-25 with ultrasound and histologically confirmed diagnosis of uterine fibroids. All women present with unexplained infertility	Menstrual bleeding (# of days, # of pads/ tampons used), rating of blood loss on a visual analog scale from 0 (no blood loss) to 10 (gushing-type bleeding), presence of side effects, overall satisfaction with treatment (5-level scale from very dissatisfied to very satisified), pain symptoms (dysmenorrhoea, dyspareunia, and pelvic pain) on a 10 point visual analog scale	Group 1 ($n=16$) received 15 mcg of ethinylestradiol + 60 mcg of gestodene, Group 2 ($n=23$) received 20 mcg of ethynilestradiol + 100 mcg of levonorgestrel, and group 3 ($n=16$) received placebo (oral calcium)	3 months		Oral contraceptive use for 3 months post surgery effectively prevents pregnancy and allows for faster improvement of clinical symptoms following myomectomy
Teixeira 2017	Brazil	Urban	RCT	50	Use of oestrogen to reduce pain related to endometriosis	Women with pain associated with deep endometriosis lesions which has not responded well to conventional therapies (hormonal therapies, nonsteriodal anti-inflammatory drugs)	Changes in severity of pelvic pain determined by modifications of the VAS score for 5 modalities of EAPP (dysmenorrhoea, deep dyspareunia, noncyclic pelvic pain, cyclic bowel pain and/or cyclic urinary pain). Secondary outcomes include scores for quality of life, assessed using the SF-36 Health Survey Questionnaire; Depressive symptoms using the Beck Depression Inventory, and axious symptoms on the Beck Anxiety Inventory.	Participants received potentized oestrogen ($n=23$) (12 cH, 18 cH, or 24 cH) (Verum). Participants were evaluated by the physician-investigator every 8 weeks (visits 2,3,4) for the duration of the study. Dose administered as 3 drops twice daily (every 12 h). Participants in the placebo group received identical vials containing hydroalcoholic solution.	24 weeks	Depression symptoms (BDI score) showed significant improvement in the potentized oestrogen group only (MD 11.53; 95% CI 4.16- 18.90; $p<0.001$). Anxiety symptoms (BAI score) showed significant improvement in both groups (MD 5.43; 95% CI 2.11-8.74; $p=0.001$) Regarding quality of life, the potentized oestrogen group exhibited improvement in three out of eight SF-36 domains: bodily pain (MD 13.71; 95% CI −25.49 to −1.92; $p=0.013$), vitality (MD −13.82; 95% CI −26.38 to −1.27; $p=0.022$), and mental health (MD −14.35; 95% CI −27.58 to −1.12; $p=0.025$). Placebo group showed no significant improvement	Baseline scores differed between treatment and placebo groups.

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Uysal 2018	Turkey	Kayseri Education and Research Hospital in Turkey	Randomised Clinical Trial	99	To evaluate and compare pain relief provided by oestradiol valerate/ dienogest and ethinylestradiol/ drospirenone using uterine artery Doppler indices and visual analogue scale (VAS) scores.	Nulliparous patients aged 18–35 years with symptoms of severe Primary Dysmenorrhoea requesting contraception were included in the study. PD was diagnosed clinically. The characteristics of pain were defined as periodic (over at least three menstrual cycles) midline, lower abdominal cramps or a pelvic colic-like pain that started up to one day before menses, lasted for three days of bleeding, gradually diminished over 12–72 h and ended after the period	Doppler indices including systolic/diastolic (S/D) rates, pulsatility index (PI) and resistance index (RI) were evaluated and recorded in both uterine vessels. Both VAS scores and Doppler indices were repeated after 3 months of OCP treatment. The changes in values were recorded.	Group 1: Control, Group 2: were administered oestradiol valerate/ dienogest. Qlarista consists of 28 tablets (two tablets of 3 mg oestradiol valerate, five tablets of 2 mg oestradiol valerate plus 2 mg dienogest, 17 tablets of 2 mg oestradiol valerate plus 3 mg dienogest, two tablets of 1 mg oestradiol valerate and two nonhormonal tablets as placebo). Group 3: 0.03 mg ethinylestradiol and 3 mg drospirenone (21 tablets). Patients were randomly administered to treatments in a 1:1 ratio. Patients were not allowed to use rescue medications (NSAIDs) to prevent menstruation-related pelvic pain	3 months	VAS scores were significantly lower in both treatment groups after 3 months of OCP therapy (p = .0001). There was no significant difference in mean percentage change of VAS scores between groups (p ¼ .32). There were lower VAS scores in both treatment groups; however, there was no superiority between these OCPs. Both oestradiol valerate/dienogest and ethinylestradiol/ drospirenone relieve pain in severe PD. Serious adverse effects were not observed in the treatment groups. The mean value of resistance index was significantly lower after therapy in Groups 2 and 3 in the right and left uterine arteries (p ¼ .001 and p ¼ .039, respectively)	The authors concluded that oestradiol valerate/dienogest, which is a routinely prescribed drug for heavy menstrual bleeding in women who desire oral contraception, is as effective as ethinylestradiol/ drospirenone in pain relief. In this study, although there was no superiority in pain relief between the treatment groups, lower VAS scores and lower RI values of uterine arteries were seen after treatment. Both OCPs relieve pain in severe PD. There was no serious adverse effect in the patients.

(*Continued*)

Table 1. Continued.

Study (year)	Country	Study setting (public / private or rural/ urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Intervention (RCTs)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Yu 2018	China Philippines, Thailand, Russia, Taiwan	Multicentre study	Randomised Clinical Trial	341	To investigate the efficacy and safety of oestradiol valerate (EV)/ dienogest (DNG) for the management of heavy menstrual bleeding (HMB) in Asian and non-Asian women desiring contraception	The main inclusion criteria for this study were as follows: women (age ‡18 years) generally in good health requesting contraception, diagnosis of HMB without organic pathology, defined as the presence of ‡2 bleeding episodes each with blood loss volume of ‡80 mL (determined by alkaline haematin method), and no evidence of malignancy/ atypical hyperplasia/ complex hyperplasia confirmed by cervical smear and endometrial biopsy within 6 months of enrolment in the study. If women were aged >40 years at enrolment, they were required to have follicle-stimulating hormone levels of <40IU/L.	The primary efficacy endpoint was the absolute change from baseline in menstrual blood loss (MBL) volume from the run-in phase to the efficacy phase. Secondary efficacy endpoints included the proportion of women with successful treatment, defined as no episode with MBL of ‡80 mL and decrease to a value of <50% of MBL of the run-in phase, the percentage change in MBL from the run-in phase to the efficacy phase, the absolute change in MBL after each treatment cycle, and the change in haemoglobin and serum ferritin concentrations on days 84 and 196. Other efficacy outcomes included number of sanitary items used during the study and the number of bleeding days.	Group 1: one film-coated tablet of EV/ DNG daily to be taken orally for seven cycles, with no tablet-free interval between consecutive cycles. Group 2: Placebo. The first dose was to be taken on the first day of bleeding following randomisation and the last dose taken on day 196.	196 days	Mean reduction in MBL volume from run-in phase was significantly greater with EV/DNG than placebo (366.75 mL vs. 149.14 mL; $p < 0.0001$), with *52% and 12% of women, respectively, experiencing successful treatment. Percent decrease in MBL volume from the run-in phase was significantly greater with EV/ DNG than placebo (63.5% vs. 24.8%; $p < 0.0001$). Haemoglobin and serum ferritin levels were increased with EV/ DNG compared with placebo.	The authors concluded that EV/DNG may be a safe and effective option in the treatment of HMB in Asian and non-Asian women who desire contraception.

Table 2. Characteristics of observational studies.

Study (year)	Country	Study setting (public /private or rural/urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Exposure (observational studies)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Abraham 2003	Australia	Family doctors	Cohort study	119	To examine the cyclicity and group differences in daily menstrual cycle mood and physical experiences of three groups of 'healthy women' using monophasic, triphasic OC or non-hormonal contraception, and to investigate the interaction of follicular depression scores with premenstrual and menstrual exacerbation of experience ratings.	Women English speaking, aged 18-41 years and had regular menstrual cycles (23-35 days)	Menstrual cycle experiences were recorded prospectively using a daily diary, containing 15 physical experiences scored from absent (0) to very severe (5), 6 mood experiences scored from absent (0) to present all the time (9), and 2 general experiences scored from absent (0) to very severe (5)	Monophasic OC (30 pg ethinylestradiol and 150 pg levonorgestrel, monophasic group), triphasic OC (30/40/30 pg ethinylestradiol and 50/75/125 pg levonorgestrel, triphasic group) or no hormonal contraception (and no intrauterine device, non-OC user group)	2 complete menstrual cycles	There were no significant differences between the three groups in cyclic changes for any physical rating, but there were for tiredness or fatigue (non-OC users reported experiencing tiredness or fatigue more frequentiy than the OC users) and sadness or depression (non-OC users experienced sadness or depression less frequently than OC users during the early part of the cycle, followed by a sharp rise from early premenstrual to the menstrual phase). There were no significant cyclic differences in ratings between the monophasic and triphasic groups.	
Driak 2017	Czech Republic	Unknown	Randomised, controlled, single-blind prospetive observatinoal study	129	To investigate the changes in uterine fibroids after exposure to low-dose combined oral contraceptives with progestin dominancy.	Females of fertile age diagnosed with single or multiple uterine fibroids.	Changes in fibroids (regression or growth) was the primary outcome. Myoma size, menstruation irregularity, and continuation of or worsening of heavy bleeding were assessed. Abdominal pain and volume of myomas were noted.	Monophasic combined oral contraception (COC) containing 20 mcg of ethinylestradiol and 75 mcg of gestodene for 21 days with no hormone therapy for 7 days.	2-4 years	In the intervention arm, myoma volume dropped significantly (from a mean of 35.3 mm to 30.2 mm, $p = 0.040$) over two years, while the mean myoma volume of the placebo group did not change significantly ($p = 0.714$).	Authors concluded that low-dose hormonal contraceptives with progestin dominancy can reduce myoma volume significantly.

(*Continued*)

Table 2. Continued.

Study (year)	Country	Study setting (public /private or rural/urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Exposure (observational studies)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Mabrouk 2011	Italy	Tertiary care university hospital	Retrospective cohort study	106	To estimate the effect of combined oral contraceptives (COCs) in women with deep infiltrating endometriosis	Females 20-40 years old	Presence and intensity of dysmenorrhoea, dyspareunia, chronic pelvic pain, and dyschezia were the primary outcomes. Nodule diameter and quality of life were also evaluated.	Cyclic combined oral contraceptives (COCs), 3 mg drospirenone and 20 mcg ethinilestradiol for 21 days and no hormone therapy for 7 days.	28 days	In COC users, VAS scores for dysmenorrhoea (p=.90)and dyspareunia (p=.55)did not vary significantly during the preoperative period. In nonusers, VAS scores for dysmenorrhoea (p=.002)and dyspareunia (p=.005) were significantly higher at the second examination than at the first examination.	Authors concluded that the introduction of COCs can reduce dysmenorrhoea, dyspareunia, and the growth of deep endometriotic nodules.
Marshall 1998	United States	Nurses' Health Study II cohort members from 14 states in the US mailed in questionnaires in 1989, 1991, and 1993.	Prospective cohort study	95,061	To investigate the risk of uterine leiomyomata in relation to reproductive factors and oral contraceptive use.	Female nurses 25–42 years old with intact uteri and no history of diagnosed uterine leiomyomata or cancer in 1989.	Incidence of self-reported uterine leiomyomata confirmed by ultrasound or hysterectomy	Oral contraceptive use (never/ current/past use, duration of use, years since last use, and age at first use).	Surveys were completed in 1989, 1991, and 1993.	Women who first used oral contraceptives between 13–16 years of age had an elevated risk of uterine leiomyomata (RR 1.26; 95% CI 1.05–1.51), and strongly increased risk of a hysterectomy- (RR 1.90; 95% CI 1.29– 2.79).	Authors concluded that oral contraceptive use and reproductive factors at a young age influence the risk of uterine leiomyomata among females aged 25-42 years.
Milsom 1990	Sweden	Urban	Prospective cohort study	489	To evaluate possible differences between different oral contraceptive combinations regarding the prevalence and severity of dysmenorrhoea	Young women from an urban Swedish population	The severity of dysmenorrhoea was assessed by a verbal multidimensional scoring system which graded the severity of dysmenorrhoea taking into account the effect on daily activity and analgesic requirements, and by a linear analogue scale.	Oral contraceptives	5 years	The severity of dysmenorrhoea was lower in users of monophasic OCs with low gestagen activity ($p < 0.001$), users of progestogen-dominated monophasic OCs ($p < 0.001$) and users of triphasic OCs ($p < 0.001$), compared to women who used neither OC nor an IUD.	

(*Continued*)

Table 2. Continued.

Study (year)	Country	Study setting (public /private or rural/urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Exposure (observational studies)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Shy 1992	United States	Group Health Cooperative of Puget Sound.	Population-based observational cohort study	7,253	To investigate tubal sterilisation and subsequent hospitalisation for menstrual disorders.	Females 20-49 years old between 1968 and 1983.	Hospitalisation for menstrual disorders.	Tubal sterilisation.	16 years (1968-1984)	Women who underwent tubal sterilisation had greater risk of hospitalisation for menstrual disorders (RR 2.4; 95% confidence interval 2.0 to 2.9).	Authors concluded that tubal sterilisation is associated with an increased risk of hospitalisation for menstrual disorders, however, no biologic association is supported by these results.
Takamura 2009	Japan	Women's Hospital at the Zhejiang University School of Medicine	Retrospective observational cohort study	311	To evaluate the impact of post-operative oral contraceptives (OCs) use on the rate of recurrence after laparoscopic excision of ovarian endometrioma.	Females who underwent a laparoscopic excision of ovarian endometrioma performed at the University of Tokyo Hospital between May 2005 and August 2006 were included.	Endometrioma recurrence, American Society for Reproductive Medicine score, cyst diameter, post-operative pregnancy and pain were noted.	Cyclic, monophasic OC containing ethinyl-oestradiol (0.035 mg) and norethisterone (1.0 mg) (Ortho-M 21w, Mochida, Tokyo, Japan), starting in Days 1 – 5 of the first menstrual cycle after the laparoscopy.	2 years	Post-operative OC-use is associated with lower endometrioma recurrence (OR 0.054; 95% CI 0.007–0.429).	Authors concluded that postoperative OC use significantly reduces endometrioma recurrence 24 months following laparoscopic excision.
Taskomur 2021	Turkey	Amasya Sabuncuoglu Serefeddin Training and Research Hospital	Cohort study	220	To investigate the long-term effects whether tubal ligation performed during caesarean had an effect on dysmenorrhoea, dyspareunia, menstrual pattern, and hormones.	Patients who underwent caesarean section five or more years ago	Dysmenorrhoea, dyspareunia symptoms and menstrual cycle patterns.	Tubal ligation	More than 5 years	There was no significant difference between the hormone levels and dysmenorrhoeadyspareunia evaluations of both groups ($p > 0.05$). However, it was found that menstrual cycle irregularity was higher in the group that underwent tubal ligation and this difference was statistically significant ($p < 0.05$).	

(*Continued*)

Table 2. Continued.

Study (year)	Country	Study setting (public /private or rural/urban)	Study design	Sample size	Study aim	Population	Outcome (s) of interest	Exposure (observational studies)	Period of observation (weeks, months, years)	Findings (effect size and 95%CI)	Note
Wang 2020	China	Tertiary care university hospital	Retrospective observational cohort study	451	To evaluate the levonorgestrel-releasing intrauterine system (LNG-IUS) to prevent the recurrence of endometrial polyps (EPs) after hysteroscopic polypectomies in premenopausal female patients.	Premenopausal females who underwent hysteroscopic polypectomies at the Women's Hospital at the Zhejiang University School of Medicine from January 1, 2016, to December 31, 2017 were included.	Endometrial polyp recurrence, polyp size, number of polyps, previous history of polypectomy, and abnormal uterine bleeding were noted.	LNG-IUS that released 20 mg LNG a day.	3 years	LNG-IUS use was strongly associated with decreased risk of endometrial polyp reccurrence (RR 0.218; 95% CI 0.089 – 0.535).	Authors concluded post-operative LNG-IUS reduces the risk of endometrial polyp reccurrence in premenopausal patients.

as well as recovery of baseline menstrual pattern, which relates to complications before using hormonal contraception. Although no language restrictions were imposed during the search, all included studies were in English (Table 3).

Quality Assessment

All included studies were assessed and ranked for quality. Details on this assessment are provided in Appendix IV. (see also Table 4).

Randomised clinical trials

Menstrual problems

Meta-analyses were possible for a wide array of menstrual problems, including recovery of baseline menstrual pattern (or, as authors noted, complete recovery), amenorrhoea, menstrual blood loss measured by haemoglobin (g/l), or menstrual bleeding using other tools, namely, 'pictorial blood loss assessment score'. The severity of menstrual signs was reported as 'daily reporting of severity of menstrual symptoms' by several authors.

Recovery of baseline menstrual pattern

Jensen 2011 [21] studied the effect of Oestradiol Valerate and Dienogest on heavy menstrual bleeding for 28 days in an RCT. Responders were defined as participants with no abnormal bleeding symptoms and achievement of all relevant criteria during the 90-day efficacy interval, and they were compared with non-oral contraceptive pill (OCP) users. The same definition was used by Fraser 2011 [22]. The following analysis is shown in Figure 2. The risk ratio was reported at 14.94 (95% CI 4.79, 46.65), although the wide confidence interval should be acknowledged when interpreting this result.

Dysfunctional uterine bleeding

Five RCTs presented data on dysfunctional uterine bleeding or irregular menstrual bleeding, two of which included specific populations of women who had fibroids [23–27]. Compiling the data was possible due to the common symptoms experienced by these women. The effect size

Table 3. Global distribution of studies.

Region	Number of studies	Studies (name of author, year of publication)
Africa	0	
Asia	12	Bagaria 2009; Chen 2017; Harada 2008; Harada 2011; Harada 2016; Harada 2017; Harada 2021; Irahara 2020; Lang 2018; Osuga 2020; Takamura 2009; Wang 2020
Americas	11	Carbonell 2016; Carbonell Esteve 2013; Catherino 2017; Davis 2000; Esteve 2013; Fiscella 2006; Hendrix 2002; Jensen 2011; Marshall 1998; Shy 1992; Teixeira 2017;
Eurasia	12	Capmas 2021; Cucinella 2013; Donnez 2012; Driak 2017; Engman 2009; Harrison 2000; Mabrouk 2011; Milsom 1990; Muzii 2000; Petraglia 2009; Taskomur 2021
Middle East	5	Barati 2015; Mehdizadeh Kashi 2022; Niakan 2021; Parsanezhad 2003; Uysal 2018
Oceania	1	Abraham 2003
Combined	4	Barlow 2014; Fox 2019; Fraser 2011; Yu 2018

reported in Figure 3 is 1.31 (95% CI 1.09, 1.58) with the expected high heterogeneity ($I^2 = 93\%$). When Davis and colleagues' study was removed, the heterogeneity was reduced to 0%, and the effect measures remained on the same side of the line of no effect (2.52, 95% CI 1.88, 3.37).

Two RCTs [21, 22] also reported on the outcome of irregular menstrual bleeding as the change in total days during which patients experienced spotting and bleeding, compared to baseline data for users of contraceptives compared to a placebo group (Figure 4).

Amenorrhoea

Three studies have been reported to study the impact of OCPs on amenorrhoea [24, 28, 29]. The time frame for these studies was approximately the same (three months or less). The effect size in Figure 5 reported 2.64 (95% CI 1.86, 3.73) in favour of the placebo group. High heterogeneity is of great concern in this analysis ($I^2 = 99\%$).

Menstrual blood loss

Menstrual blood loss was measured by the Pictorial Blood Loss Assessment Chart (PBAC). A 2021 study by Ko et al. determined that a PBAC cut-off score of 76 has a sensitivity of 93.2% and specificity of 83.0% for the prediction of self-perceived heavy menstrual bleeding [30]. A PBAC score <75 was used as a primary endpoint in two studies comparing the use of 10 mg UPA to a placebo, and a cut-off score of <60 was used in one study with the same intervention. The risk ratio of 7.12 (95% CI 2.33, 21.76) is shown below in Figure 6. These authors also provided data on PBAC scores at the end of treatment, with an SMD of −0.58 (95% CI −0.91, −0.25), as seen in Figure 7. Donnez et al. 2012 reported that 70% of patients in the 10-mg group were amenorrheic within the first ten days of the study, which explains the mean PBAC score of 0 for this intervention group [28].

Three RCTs (whose OCP users were on all combined hormonal contraceptive pills) tracked the participants' mean blood loss (mL) from baseline to the end of treatment through the collection of sanitary items used [21, 22, 31]. The SMD was reported to be 0.81 (95% CI 0.64, 0.98), as seen in Figure 8 below.

Six studies also measured Menstrual blood loss in haemoglobin level (g/dL) [21, 22, 24, 29, 31, 32]. In Figure 9, SMD was reported to be 0.20 (95% CI 0.04, 0.36) with a low heterogeneity of 27%, referring to a low variability.

Menstrual symptom severity

Three studies used the 'daily reporting of severity of menstrual symptoms' scale to study the severity of menstrual symptoms [33–35]. The SMD for these studies in Figure 10 shows that compared to OCP non-users, OCP users had a −1.20 lower SMD (95% CI −1.36, −1.03). A lower severity score means less/less severe menstrual symptoms.

Menstrual symptoms using general tools

Fox 2019 reported menstrual pain as a continuous variable using the 'Dysmenorrhoea Daily Diary', which captured vaginal bleeding, cramping pain score, rescue pain medication use, and the impact of pelvic pain on daily life [36]. Hendrix used a similar tool called the 'Mood Disorder Questionnaire'

Table 4. Modified dawn and black assessment for observational studies.

Author, year	Reporting	External validity	Internal validity		Total score
			Bias	Confounding	
Abraham 2003	5	1	5	2	13
Driak 2017	4	0	4	1	9
Mabrouk 2011	5	1	3	2	11
Marshall 1998	5	2	5	3	15
Milsom 1990	5	2	4	2	13
Shy 1992	5	1	5	3	14
Takamura 2009	4	1	3	3	11
Taskomur 2021	5	1	4	2	12
Wang 2020	6	2	5	3	16

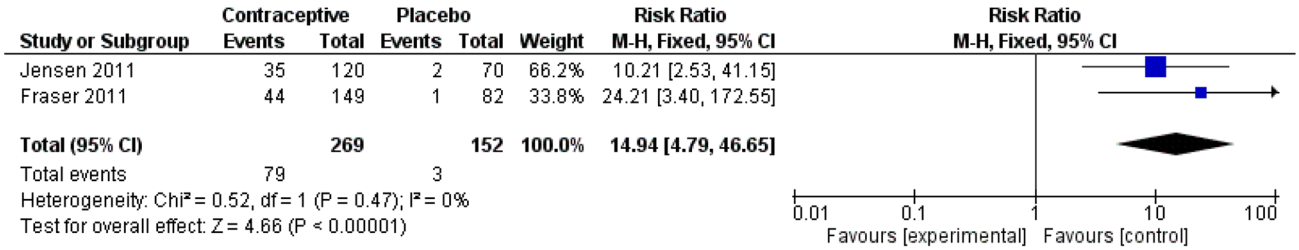

Figure 2. Recovery from abnormal bleeding, for the type of hormone, refer to the table of included studies.

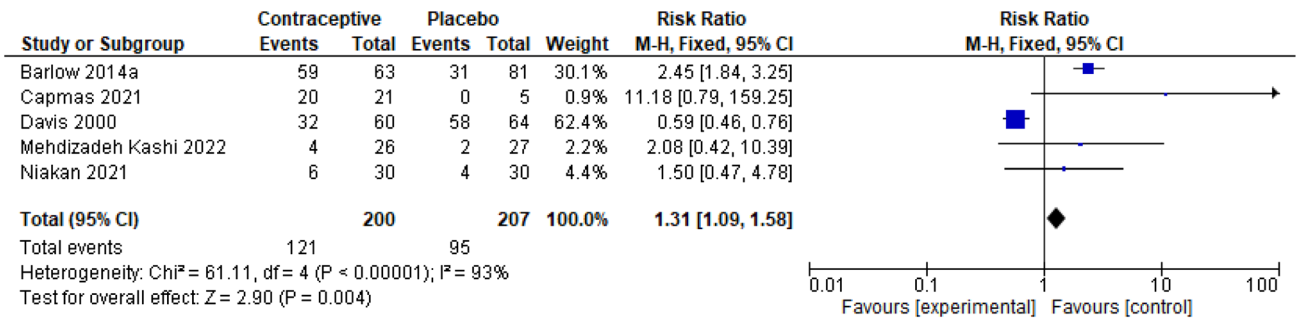

Figure 3. Irregular menstrual bleeding (events), for the type of hormone, refer to the table of included studies.

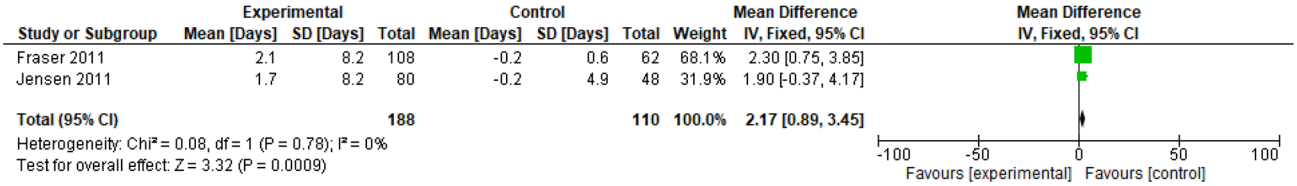

Figure 4. Irregular bleeding (days), for the type of hormone, refer to the table of included studies.

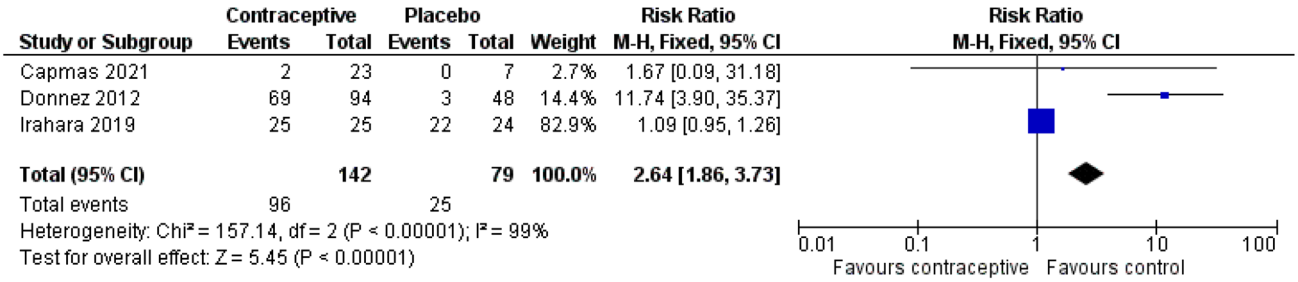

Figure 5. Amenorrhoea, for the type of hormone, refer to the table of included studies.

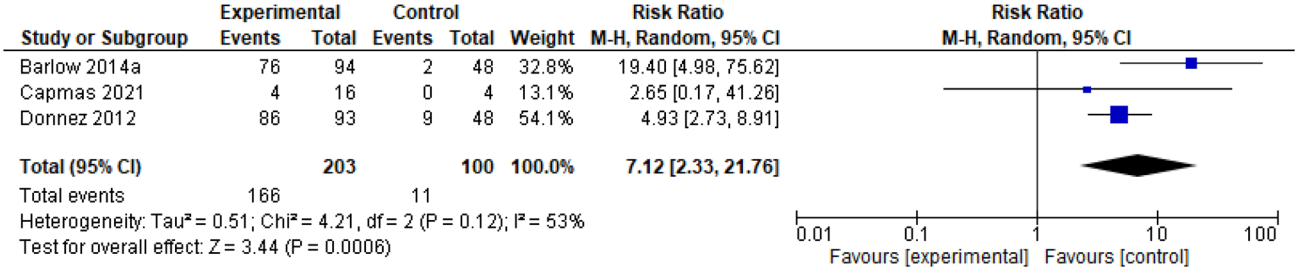

Figure 6. Final PBAC score <75, for the type of hormone, refer to the table of included studies.

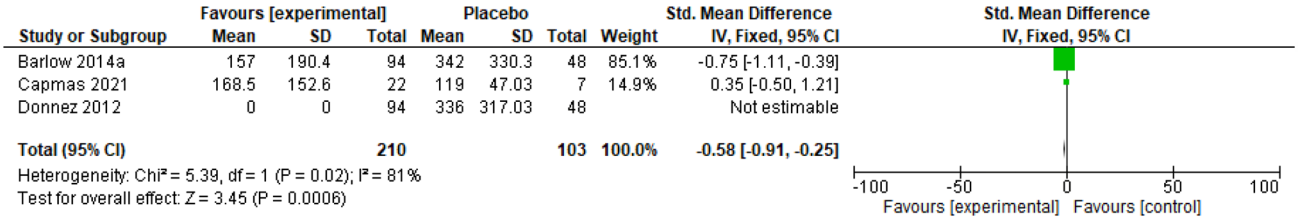

Figure 7. Final PBAC scores, for the type of hormone, refer to the table of included studies.

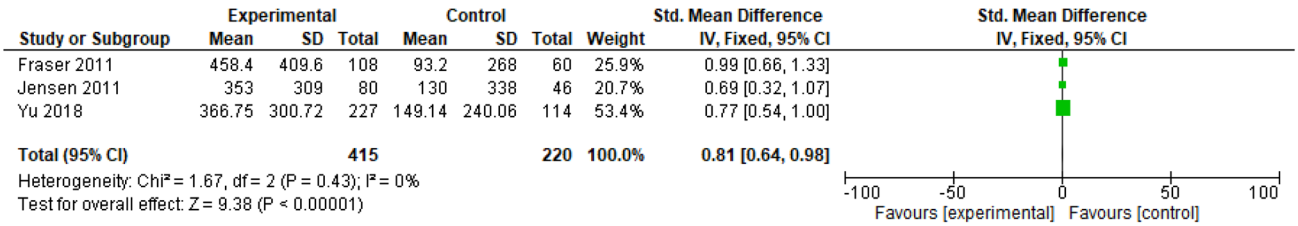

Figure 8. Change in mean blood loss (mL), for type of hormone, refer to the table of included studies.

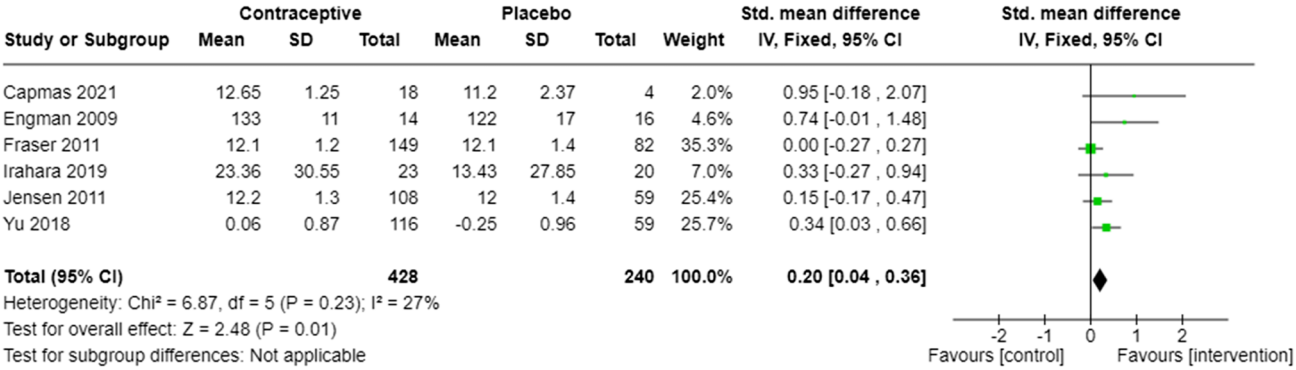

Figure 9. Haemoglobin level (g/dL), for the type of hormone, refer to the table of included studies.

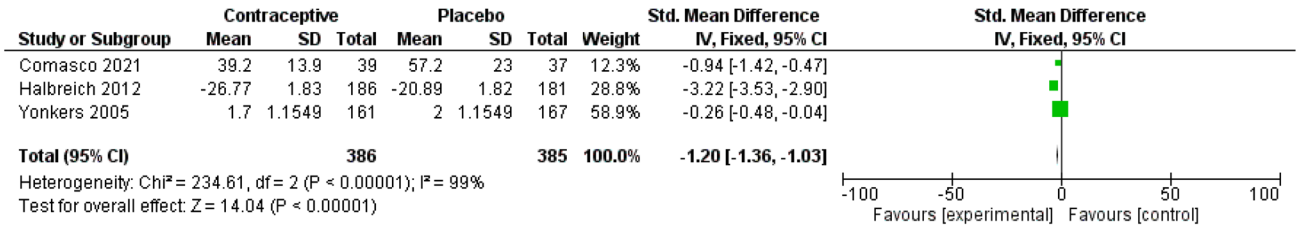

Figure 10. Severity of menstrual symptoms, for the type of hormone, refer to the table of included studies.

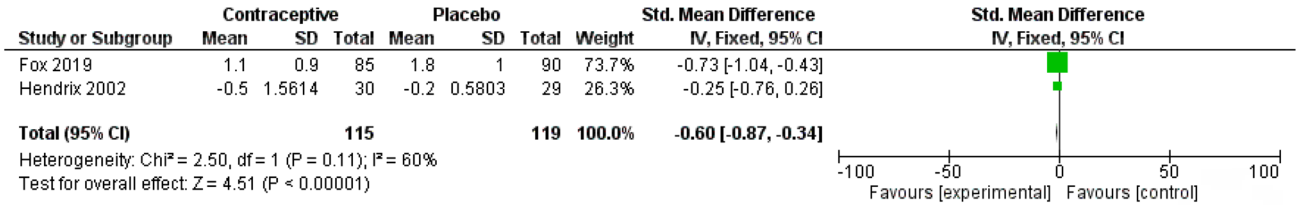

Figure 11. Menstrual pain score, for the type of hormone, refer to the table of included studies.

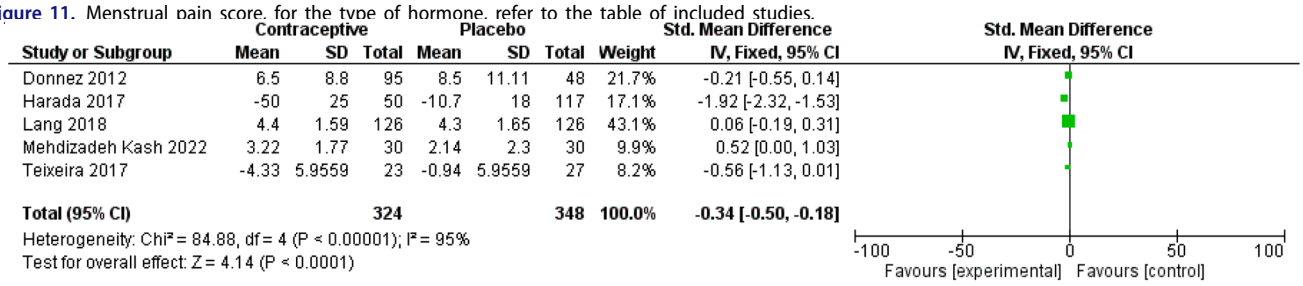

Figure 12. Endometriosis associated with pain (mean scores), for the type of hormone, refer to the table of included studies.

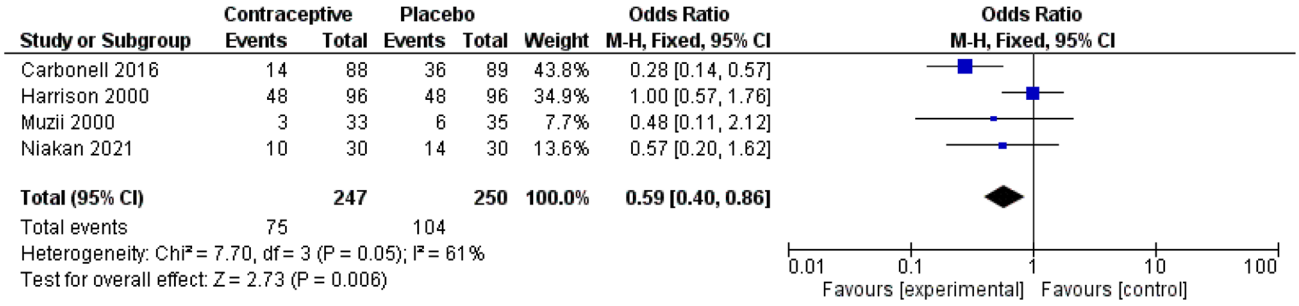

Figure 13. Endometriosis associated with pain (events), for the type of hormone, refer to the table of included studies.

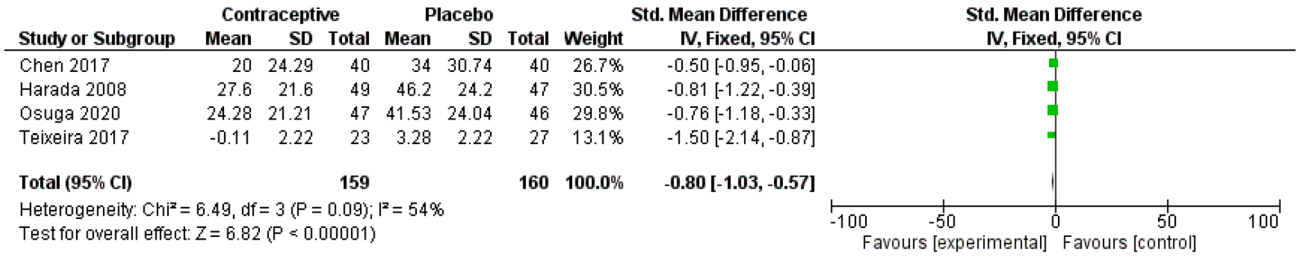

Figure 14. Dysmenorrhoea associated with endometriosis; for the type of hormone, refer to the table of included studies.

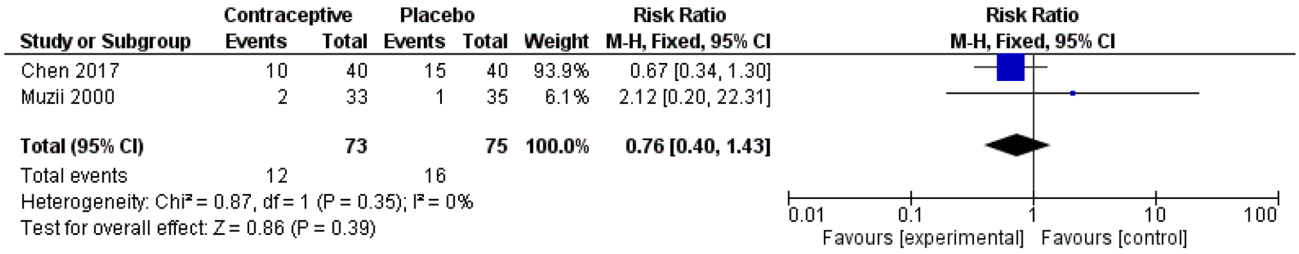

Figure 15. Endometriosis recurrence, for the type of hormone, refer to the table of included studies.

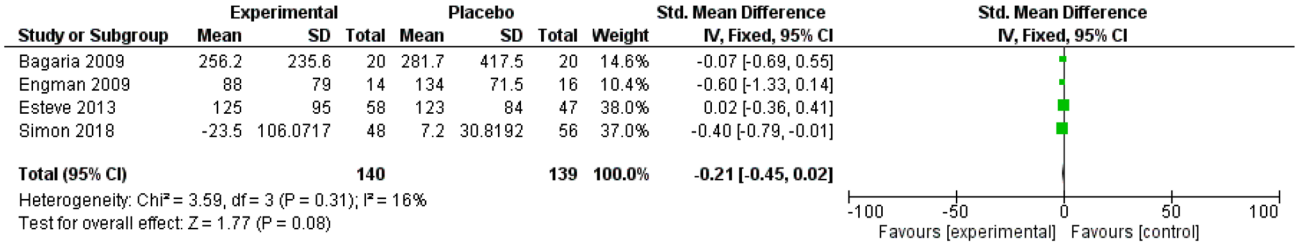

Figure 16. Leiomyoma size, for the type of hormone, refer to the table of included studies.

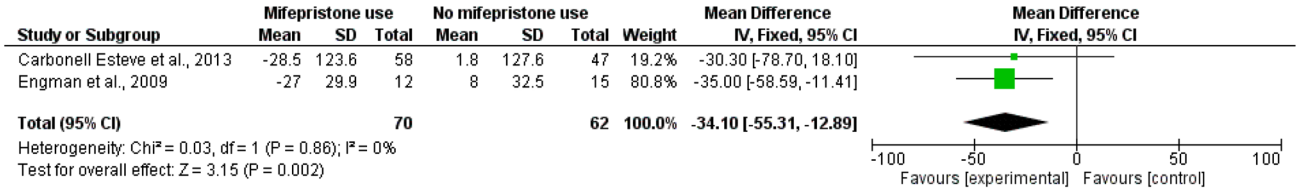

Figure 17. Myoma volume (mL), for the type of hormone, refer to the table of included studies.

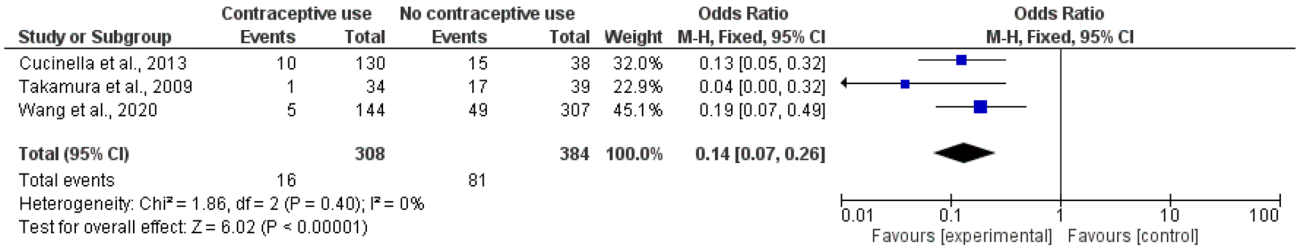

Figure 18. Endometriosis reoccurrence, for the type of hormone, refer to the table of included studies.

[37]. This questionnaire consists of 47 questions regarding symptoms experienced during menses. Each answer is scored from 0 to 4, with 0 being no experience of symptoms and four being severe. The questions cover eight subscales for distress, including pain, water retention, autonomic reactions, negative effects, impaired concentration, behaviour change, arousal, and control. The effect size in Figure 11 shows a reduction in SMD among OCP users compared to non-users of −0.60 (95% CI −0.87, −0.34) with a moderate heterogeneity level of 60%, which may relate to the self-reported measure.

Endometriosis

Pain associated with endometriosis

OCPs are often used for symptom management as well as family planning in individuals with endometriosis. Several RCTs were dedicated to this concept, and there were abundant comparisons between OCP users and non-users. Pain due to endometriosis, dysmenorrhoea, and dyspareunia were found to be among the most reported outcomes.

Five studies reported pain associated with endometriosis as a continuous variable. Lower pain was reported for OCP users compared to non-users (SMD: −0.34, 95% CI −0.50, −0.18) in Figure 12. Heterogeneity in this analysis was high (I^2=95%), possibly due to various pain measurement tools [26, 28, 38–40].

Four studies also reported pain as a dichotomous variable [4, 27, 41, 42]. Like other meta-analyses on pain as a continuous variable, this analysis showed a lower pain incidence among OCP users than non-users (0.59, 95% CI 0.40, 0.86). The I^2 was still relatively high (I^2=61%), which may be associated with different doses and duration of OCP between studies (Figure 13).

Dysmenorrhoea associated with endometriosis

Four RCTs were included in Figure 14 as they all reported dysmenorrhoea associated with endometriosis as a continuous variable. The risk ratio was −0.80 for SMD analysis (95% CI −1.03, −0.57) with an I^2 value of 54%, indicating a higher level of heterogeneity.

Endometriosis recurrence

Two studies also reported endometriosis recurrence, as seen in Figure 15 [42, 43]. The effect size was 24% lower among OCP users, and the 95% CI crossed the line of no effect (0.40, 1.43).

Leiomyoma size

Using OCPs reduced the size of leiomyoma (SMD: −0.21, 95%CI −0.45, 0.02). Four studies examined this relationship [32, 44–46]. Simon reported median and interquartile range, suggesting a non-normal distribution of data (Figure 16).

Uterine fibroids

Two RCT studies reported a decrease in the size of myoma volume (ml) following the use of mifepristone (one daily capsule of 5 mg mifepristone or a mifepristone placebo over 3 months for Crabonell Esteve et al. (2013) study and 50 mg mifepristone or placebo every other day during 3 months for the Engman et al. (2009) study compared to non-users. The mean difference was −34.10 with a wide confidence interval (95% CI −55.31, −12.89) and zero heterogeneity in Figure 17 [32, 47].

Cohort studies

Endometriosis

We found three cohort studies that reported prospective endometriosis recurrence among contraceptive versus non-users. Wang and colleagues (2020) investigated the LNG-IUS, and Cucinella et al. (2013) and Takamura et al. (2009) looked at the effect of oral contraceptives. As seen in Figure 18, the total number of endometriosis recurrence events among contraceptive users was 16 (out of 308) compared to 81 (out of 384) in the control group, leading to an OR of 0.14 (95% CI 0.07, 0.26) with zero heterogeneity [48–50].

Side effects of contraceptives

A significant number of side effects were reported, including, but not limited to, uterine haemorrhage, ovarian haemorrhage, menometrorrhagia, uterine bleeding, headache, abdominal pain, pyrexia, breast pain, hypercholesterolaemia, hypothyroidism, constipation, hypertriglyceridaemia, etc. Some reported side effects are the primary outcomes of interest that other trials aim to study. Although the variety of possible side effects is imposing, it has implications for future studies to elucidate their significance (see Appendix V).

Discussion

Summary of main results

The review examined the relationship between menstrual issues and various types of pain, including abdominal, pelvic, and lower back pain, associated with dysphasia. Initially, 44 studies were identified, primarily consisting of RCTs and cohort studies. For menstrual problems, RCTs focused on outcomes such as recovery of baseline menstrual patterns, dysfunctional uterine bleeding, amenorrhoea, menstrual blood loss, and symptom severity. Contraceptive users generally experienced significant improvements in these outcomes compared to non-users, although high heterogeneity was observed across some analyses. In endometriosis management, RCTs explored pain, dysmenorrhoea, recurrence rates, leiomyoma size, and uterine fibroids. Contraceptive users tended to experience reduced pain, lower recurrence rates, and smaller leiomyoma size. Cohort studies also indicated a lower risk of endometriosis recurrence among contraceptive users. However, variability in study methodologies and interventions highlights the need for further research to optimise treatment outcomes in these areas.

Agreements and disagreements with other studies

In general, our findings are similar to prior studies that have examined the association between contraceptives and non-reproductive health outcomes. Studies investigating quality of life or well-being in women with heavy menstrual bleeding, endometriosis, or uterine fibroids found improvements in all dimensions assessed, which is similar to the findings of Bürger. Our findings on dysmenorrhoea reduction have also been confirmed in a previous study conducted by Iwata and colleagues [51]. We also have strong evidence that contraceptives reduce heavy menstrual bleeding, like the results found by Lethaby [52]. For endometriosis patients, the effects of contraception on the alleviation of symptoms such as pelvic pain and dysmenorrhoea have been shown both in this paper as well as in others. A review conducted by Grandi et al. combined hormonal contraceptives and progestin-only contraceptive were found to be associated with clinically significant reductions in dysmenorrhoea [53]. Postoperative use of contraceptives was significantly associated with preventing the risk of endometriosis recurrence and pain related to endometriosis within our study, which is similar to the findings. A different study conducted by Ghonim observed that among women suffering from uterine fibroids treated by ulipristal acetate, attainment of amenorrhoea was significant, indicating an improvement in symptoms among contraceptive users [54].

Strengths

We initially searched the databases for all studies from their inception. Thus, we included studies with up-to-date contraceptive methods with broad coverage. For each outcome category, our studies covered diseases and conditions commonly seen in women of reproductive age. For some of these outcomes, we found a few studies that yielded larger pooled sample sizes, allowing for higher statistical power, narrower confidence intervals, and more credible results. In addition to the use of contraception for contraceptive purposes, we also explored the effectiveness of contraception as a treatment. This provides additional evidence for the use of contraception as a treatment in clinical settings and for reasonable insurance coverage.

Limitations

The exclusive use of studies that compare hormonal contraceptive users to a placebo group has both clear benefits and limitations. With the varying HC methods and drug dosage options available to women, it is important to identify which regimens work most effectively with minimal side effects, but our analysis does not account for these differences. Some of the regimens used across the studies include ulipristal acetate 5 mg or 10 mg, nomegestrol acetate -E2, etonogestrel-E2, oestradiol valerate/dienogest, levonorgestrel/ethinyl oestradiol, drospirenone/ethinylestradiol, and oestrogen.

The study highlighted several key points. Firstly, it emphasised the need to examine the relationship between hormonal contraceptives and duration of use, as most studies only looked at short-term effects. Longer durations may reveal different outcomes, including potential protective or harmful effects. Secondly, it pointed out limitations in assessing quality-of-life improvements due to inadequate sample sizes and heterogeneous data. Thirdly, it discussed the importance of considering gender inclusivity in research terminology, particularly in studies involving contraceptive use, where not all users identify as women. Overall, the study called for more comprehensive and inclusive research methodologies to better understand the effects of hormonal contraceptives.

Implications for research

The systematic review examined the effects of hormonal contraceptives beyond preventing pregnancy, revealing

benefits like alleviating menstrual symptoms and enhancing women's quality of life. However, it also uncovered potential long-term side effects such as increased risks of cardiovascular disease, breast cancer, and mental health issues, although these weren't the main focus. With the emergence of new contraceptive methods, more research on their non-reproductive health impacts is crucial for informed clinical decisions. Overall, the review offers valuable insights for clinical practice and policymaking, ensuring women access safe and effective contraceptive options promoting overall health. Further research implications are detailed in Appendix V.

Implications for clinical practice

Healthcare providers should view hormonal contraceptives as safe and effective treatments for heavy menstrual bleeding, endometriosis, uterine fibroids, and premenstrual dysphoric disorder. Patients should be informed about the benefits of hormonal contraception in managing pain, symptoms, and abnormal bleeding associated with these conditions, which greatly affect quality of life. Our review addresses timely issues relevant to gynecological practice, exploring less invasive and cost-effective treatments for conditions like adenomyosis and fibroids, as well as managing endometriosis. While our findings show promising clinical outcomes, some relevant studies were omitted, such as Magalhaes et al. [55] Integrating evidence from these studies could enhance treatment strategies and patient outcomes, emphasising the need for ongoing research and critical evaluation in gynecological care.

Acknowledgements

The authors would like to gratefully acknowledge comments and suggestions from the WHO Technical Advisory Group (TAG) consisting of (listed in Alphabetical order): Dr. Ann Biddlecom; Dr. Harriet Birungi; Professor Herbert Peterson; Dr. Iqbal Shah; Dr. James Kiarie; Professor John Cleland; Dr. John Townsend; Dr. Manala Makua and Professor Sonalde Desai. We would like to specially acknowledge the support and guidance by Dr. James Kiarie (WHO) throughout the process to complete the project. We thank him for his efforts. We acknowledge the support of USAID who provided input on the research questions. USAID did not participate in the data abstraction, analysis or interpretation or the decision to submit it for publication. The analysis, interpretation, write up and decision to submit the paper was coordinated by the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual and Reproductive Health and Research, WHO. All authors were consultants and one author is a staff member. Furthermore, we are grateful to Amy Lapidow for her assistance in developing the search strategies and helping us to conduct a literature search that yielded over 7,000 studies. We would also like to thank all at Tufts University School of Medicine who have supported completing this research. Many thanks go to them. A team of researchers from the Cochrane Fertility group contributed intellectually to providing support for this project. The team members are Alison Edelman, Motu Makaplapua, and Jullian Henderson.

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Disclaimer

The named authors alone are responsible for the views expressed in this publication and do not necessarily represent the decisions or the policies of the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) or the World Health Organisation (WHO).

Ethics approval

Not applicable.

Patient consent for publication

Not applicable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study received support from the USAID consolidated grant 7200GH21IO00005.

Data availability statement

No data are available.

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