ORIGINAL ARTICLE

Title: Efficacy of ulipristal acetate in women with fibroid induced menorrhagia: A systematic review and meta-analysis

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Abstract

Aim: To evaluate the efficacy of UPA in women with fibroid induced menorrhagia.

Methods: Embase, MEDLINE, CAB Abstracts, Cochrane Central Register of Controlled Trials, PsychInfo were searched up to 18th May 2020 and updated on 7th February 2021. Randomised controlled trials evaluating the efficacy of UPA in women with fibroid induced menorrhagia were included in the study.

Results: Two authors independently reviewed and extracted the study data. Statistical heterogeneity was quantified using I^2 statistics. Publication bias and data asymmetry was assessed by funnel plots. A meta-analysis was conducted where appropriate. Six studies were eligible for inclusion. UPA (5 mg and 10 mg) achieved statistically significant amenorrhoeic outcome when compared to placebo ($p<0.00001$). Increased adverse events (AE) profile was observed in the higher UPA dose, however, did not reach statistical significance.

Conclusions: This review demonstrates the efficacy of UPA in achieving amenorrhoea in women with fibroid induced menorrhagia. However, the favourable dose of UPA remains inconclusive when AE profile is taken into account. Evidence remains obscure regarding liver damage and further research is warranted to attain a conclusive outcome.

Introduction

Fibroids (uterine leiomyomas) are common benign tumours that can cause menorrhagia and dysmenorrhea [1]. Fibroids can affect fertility [2], and often have a negative impact on quality of life (QoL) with 64% of women having experienced a negative impact to QoL affecting many areas including: relationships, mental health, occupation, energy levels and body image confidence [3,4]. Ulipristal acetate (UPA) is an antagonistic progesterone receptor modulator, that helps alleviate symptoms of menorrhagia. The mechanism of UPA involves shrinking fibroids by blocking pathways of progesterone which contribute to their growth and maintenance [5].

In 2018, the European Medicines Agency (EMA) advised liver screening to be performed prior, during, and post-treatment with UPA due to the association of liver damage in long-term use. This association was made after 8 cases of serious liver injury were reported among an estimated 765,000 patients treated thus far, with UPA [6]. However, use of UPA was suspended in March 2020, as since 2018, 5 more cases of liver damage were reported with sufficient evidence of UPA being the cause despite safety measures already put in place. There was also one case reported where damage was so severe, liver transplantation was required [7]. On 12th November 2020, EMA recommended restricting the use of UPA to premenopausal women for whom surgical procedures are not deemed appropriate or have not worked [8].

Given this controversy, this systematic review contributes to the literature to evaluate the effectiveness of differing doses of UPA as a treatment for symptomatic fibroids. The primary outcome was to analyse the effects of UPA at differing doses in treating

uterine fibroid induced menorrhagia. The secondary outcome was to evaluate adverse events and the safety profile of UPA.

Materials and Methods

A systematic literature review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Fig. 1). A PICOS method (Population, Intervention, Control, Outcome, Study Type), was used to develop the research question (Supplementary table S1) [9].

Search Strategy

Independent literature search for relevant studies was conducted up to 18th May 2020 and was updated on 7th February 2021 on five databases: Cochrane Central Register of Controlled Trials (OVID), CAB Abstracts (OVID), Embase (OVID), MEDLINE(R) (OVID), APA PsycInfo (OVID). The following search terms were used in OVID: (Ella norpregnadiene or Ella or Esmya or Ulipristal Acetate or CDB-2914) and (fibroid* or fibromyoma* or myoma* or leiomyom* or uterine fibroma or uterine leiomyomata or fibroma or hysteromyoma). Searches were then restricted to randomised control trials (RCTs).

Inclusion and Exclusion Criteria

Randomised controlled trials that were conducted on women between 18 and 50 years old, with one or more symptomatic uterine fibroids, that used ≥ 2 different doses of ulipristal acetate and compared it to placebo were included. Studies which had 1) Number of participants < 20, 2) duration < 12 weeks, 3) surgical interventions, 4) postmenopausal women were excluded. No language or geographical restrictions were applied.

Study Selection

After removing the duplicates, citations were screened by title, abstract and full text appraised to determine their eligibility. Data from each article was extracted and cross checked independently by two researchers. Disagreements were solved in a consensus meeting.

Data Extraction

Data on participant demographic details, diagnosis and bleeding criteria, treatment regime, details about the intervention and control group including follow up details were extracted by two reviewers and cross-checked by a third reviewer.

Outcomes

The primary outcome was amenorrhea, defined as per Table 1 for each individual study. Secondary outcomes included safety profile and adverse events.

Quality Assessment

Six studies were critically appraised independently by two researchers, using the Cochrane Collaboration's Risk-of-Bias 2 (RoB2) checklist [10].

Data analysis and Meta-analysis

The summary of the study characteristics is presented in table 1. Adverse events as reported by each study, were collected and systematically reviewed given that a meta-analysis approach for these outcomes was not feasible given the nature of the presented data (Table 2 and Table 3). The meta-analysis was conducted by computing the risk ratio (RR) from the original data using the Cochrane-Mantel-Haenszel method. Data analysis was carried out using Review Manager (RevMan) v5.4 software (Cochrane Collaboration) using a fixed-effect (RE) model. Statistical heterogeneity was quantified using I^2 statistics and Cochrane Q tests [10]. Publication bias and data asymmetry was assessed by funnel plot symmetry (RevMan V. 5.4).

Results

Initial search retrieved 894 records via systematic building block. A total of 41 studies were eligible for full-text screening. Following the PRISMA screening protocol [11] (Fig. 1), a total of six trials [12-17] were included in the systematic review and meta-analysis (Table 1). Overall quality of studies was high with the exception of two studies [12-13] where high risk of attrition bias was detected (Fig. S1).

Study Characteristics

Across the six studies, 676 patients were enrolled and treated; 332 with 5 mg UPA, 344 with 10 mg UPA and 259 patients were allocated to receive placebo. All trials implemented participant criteria based on age, below 50 years. The minimum age was 18, with the exception of, Levens *et al*., [12], Nieman *et al*., [13] and Irahara *et al*., [15] which set a minimum age of 33, 25 and 20 years respectively. One paper had an ethnic criterion: Irahara *et al*., [15] had participants of Japanese origin. The participants within four studies were mainly of Black descent [12-14, 17]. One study contained participants mainly of Caucasian descent [16]. All studies included in this systematic review evaluated the efficacy of UPA versus a placebo control. The dose of UPA varied amongst the RCTs. All studies used 5 mg and 10 mg UPA dosages except studies by Levens *et al*., [12] (10 mg and 20 mg) Nieman *et al*., [13] (10 mg and 20 mg) and Irahara *et al*., [15] (2.5 mg, 5mg, and 10 mg). The treatment lasted 12 weeks in all RCTs with the exception of Donnez *et al*., [16] (13 weeks) and Levens *et al*., [12] (90-102 days). Simon *et al*., [14] and Irahara *et al*., [15] had an additional 12-week drug-

free follow-up period. Nieman *et al*., [13] offered selected participants an additional three-month treatment with UPA. All trials used placebo as the control drug.

Meta-analysis of Amenorrhea as Primary Outcome

All studies explored menorrhagia and quantified the amount of bleeding by using a set definition of amenorrhea in women at the end of their treatment course (either 5 mg and/or 10 mg and placebo). Results highlighted a statistically significant difference for both the doses of 5 mg and 10 mg UPA versus placebo across all trials. With amenorrhea as desired outcome, meta-analysis of all studies [N=6] favored UPA (5mg and 10 mg) over placebo [RR 23.77 (11.09, 50.93); p<0.00001) (Fig. 2). UPA 5 mg [N=4] [RR 22.43 (9.88, 50.95); p<0.00001) and UPA 10 mg [N=6] [RR 25.22 (11.88, 53.54); p: <0.00001) were similarly favoured over placebo in the subgroup analysis with I^2 of 0 (Fig. S2; Fig. S3). Risk ratio analysis of the dosage regimen of UPA, favored UPA 10 mg over 5 mg [RR 0.83 (0.73, 0.93); p: 0.002) (Fig. 3A). Nonetheless, AE profile of UPA 10 mg regimen was found to be collectively higher when compared to UPA 5 mg, however statistically not significant (Fig. 3B).

Systematic Review of Secondary Outcomes

Given that studies did not provide adjusted hazard ratios of adverse events, an inverse variance analysis was not feasible. To analyze adverse events and safety profile of UPA dosing regimens, we explored the included studies narratively.

Safety Profile and Adverse Events

The majority of papers reported higher dropout rates due to AEs within the active treatment groups compared with placebo groups (Table 2). No deaths were reported in any of the six studies. While a number of trials reported serious AEs, these were deemed to be unrelated to the treatment rather due to underlying health conditions or lack of sufficient evidence [14,15,17]. Two studies [13-14] reported higher dropout rates amongst active groups. Two studies reported no serious AEs [12, 13]. Donnez *et al*., [16] reported 7 serious AEs; three in the placebo group (protrusion of fibroid through cervix, breast cancer, menometrorrhagia) and two within both 5 mg and 10 mg groups (uterine and ovarian hemorrhages).

Liver Injury

Of the six trials analyzed in this review, four referred to liver function [13,15, 16, 17] (Table 3). Three trials used liver function tests (LFTs) to exclude participants with elevated liver enzymes, elevated bilirubin or further signs of hepatotoxicity before the trial commenced and recorded 12 cases of elevated transaminases [13, 15, 17]. It is noted that these trials excluded participants with elevated liver enzymes before UPA was administered. Eleven out of these twelve cases were confirmed to be recipients of UPA (5 mg or 10 mg), and the remaining one was recorded as a severe AE related to abnormal LFTs, however, it was not stated whether the participant was a recipient of UPA or placebo and was deemed unrelated to treatment [17]. Levens *et al*., [12] reported one case of increased aspartate transaminase/alanine transaminase that exceeded two times the upper normal rank in a patient receiving 20 mg UPA.

Discussion

The available data from this review suggest statistically significant benefits of UPA in both dose regimes (5 mg, 10 mg) over placebo in controlling menorrhagia. Furthermore UPA 10 mg was more beneficial than 5 mg by significantly improving amenorrhea outcome for the high dose exposed group. Nonetheless, AE profile of UPA 10 mg regimen was found to be collectively higher when compared to UPA 5 mg, a finding that comes in agreement with the recent EMA recommendations regarding UPA safety. The findings support the use of lower UPA doses, if necessary when assessing risk/benefit in patient management. Whilst statistically significant regarding achieved amenorrhoea, the difference of UPA doses, need to be primarily examined under the spectrum of patient safety.

Overall, there is limited evidence data on adverse events to definitively conclude a favorable dosage. From the present work, there are insufficient evidence to conclude if UPA has non-reversible, adverse effect on liver function. The patient numbers with reported raised transaminases among studies were minimal. Whether the observed elevation in hepatic enzymes warrants a suspension of the drug, given the benefits, requires further investigation [21]. Of note, no trials were performed on women with underlying health conditions such as injury to the liver, and thus a definite conclusion cannot be made acknowledging whether the benefits of this drug outweigh its risks. Further exploration of UPA on women within these specific criteria is warranted.

Limitations

A limitation of this review is the applicability of the results to the United Kingdom (UK) population. Most of the research was conducted across the United States, Japan and within European (EU) countries. Each study had a varying number of research centers which ranged from 38 to 53 with only one study having a research center based within the UK [16]. All studies used self- reporting of spotting or no bleeding to assess amenorrhea. One study made use of the Pictorial Blood Assessment Chart (PBAC) score, trusting participants to accurately report their level of bleeding to a scale [16]. This could have led to potential participant bias if results were reported inaccurately or in favor of the desired result. A limitation of all studies within the review was their restricted time scale and lack of measures for assessing long term effects (Table 1). Although this timescale was more than adequate to highlight drug efficacy, it may not have been lengthy enough to evaluate long-term effects of UPA.

Strengths

Our results are consistent with a previous systematic review conducted in December 2018 [18]. The main strength of this systematic review and meta-analysis is provided by its methodology. A PICOS method was used to develop the review question and identify key elements. Thorough search across five databases was performed to identify suitable papers alongside the formulation of inclusion and exclusion criteria. Dual critical appraisal of studies according to Cochrane standardized checklist was conducted with any disagreement being resolved among all authors. This methodological approach was adopted to strive for consistency, minimize selection

bias and strengthen the review. All studies included in the review had a primary common outcome of achieving amenorrhea with comparison arms UPA vs. placebo. This allowed for consistent comparisons to be made between the studies in order to achieve this review's primary outcome. Meta-analysis of the total of six studies provided collective and comparative data strengthening the statistical significance of the assessed outcome. Subgroup analysis of UPA doses in view of amenorrhea provided further insight in the scaled response to UPA. Adverse events were sought and recorded to provide a holistic picture of both the efficacy but also the safety profile of UPA.

Implications for Future Research

In light of the recent EMA recommendations [8] for the management of uterine fibroids, there remains few non-surgical options for women suffering with this condition. Therefore, there is a need to fill this gap in service provision by finding an alternative treatment with similar efficacy as UPA, but without the serious risk of harm. Future studies should focus on understanding the mechanism behind UPA causing acute liver injury (ALI), whilst also considering whether any specific demographics of women are more vulnerable to these AEs. Some studies considered in this report were limited due to failure of measuring and evaluating LFTs of participants. Future studies should address this by measuring ALT, AST, GGT and bilirubin levels as part of the follow up procedure, as such tests are essential indicators of potential ALI.

Conclusions

In summary, this review adds to the existing literature on the effectiveness of UPA's in treating women with uterine fibroid induced menorrhagia and achieving amenorrhea. It appears that there is a correlation between the dosage of UPA and the number of AEs. However, it is unclear of the favourable dose when AE profile is taken into account. Future adequately powered trials with long-term follow -up are required to evaluate the effectiveness of different doses on the overall QoL and discovering the optimal dosage, weighing up the benefits and risks of achieving amenorrhea. There is a lack of evidence to further suggest liver damage in women. Additional research is recommended to attain a conclusive outcome. This review indicates further research to identify the effects of various doses of UPA on the liver within different groups, and thus whether it is a viable long-term treatment option for all women.

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Author Contributions

All authors contributed to the study design. LB, GK, DM contributed to article screening, and study selection. EB, AG, GK, GU, contributed to data extraction and synthesis. EB, LB, TRB, AG, GK, DM, GU contributed to the quality assessment of the studies. SLK and GK analyzed the data. GK drafted the manuscript. AP and AJ provided expert opinion. All authors provided comments on early drafts and approved the final manuscript.

Declaration of Competing Interest

Authors have no completing interests to disclose.

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Figures

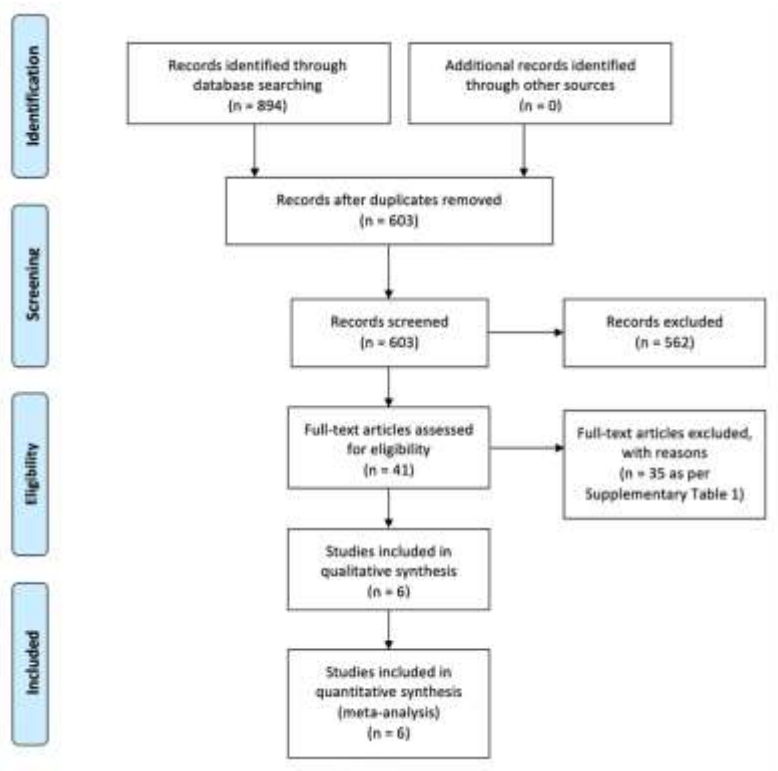

Fig. 1. PRISMA 2009 Flow Diagram

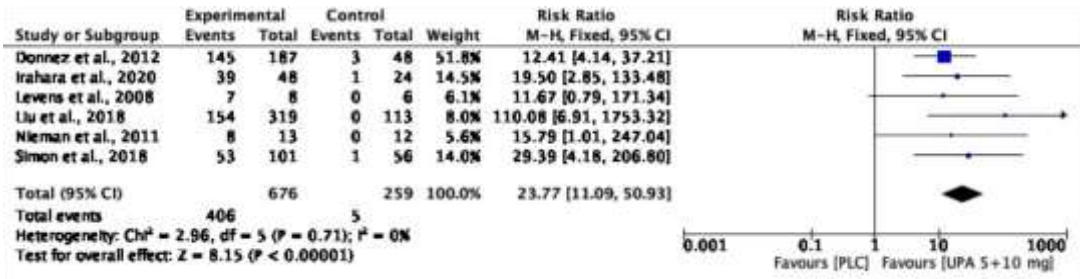

Fig. 2. Forest plot Ulipristal acetate (5 and 10 mg) vs. Placebo; Outcome Amenorrhoea

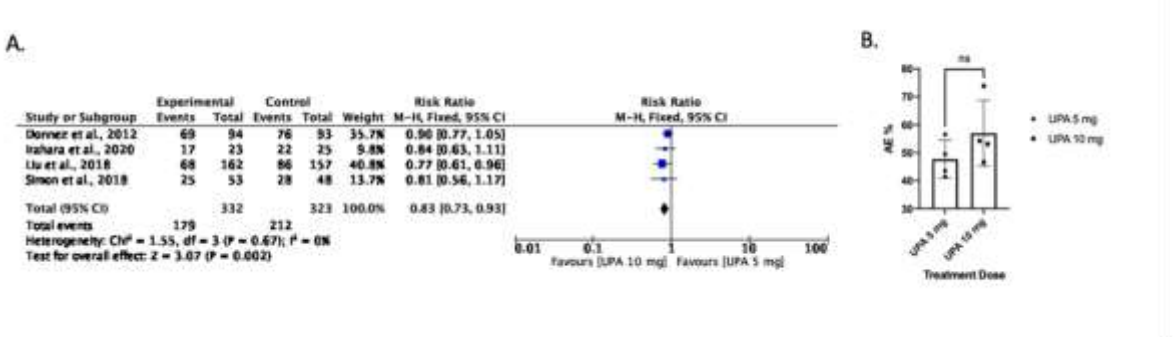

Fig. 3 A. Forest plot Ulipristal acetate (10 mg) vs Ulipristal acetate (5 mg); Outcome Amenorrhoea (B) Overall adverse event (AE) profile of UPA (5 mg and 10 mg)

Table 1 Summary of study characteristics in the reviewed studies UPA = Ulipristal Acetate

	Age Range (years)	Cohort	Diagnosis	Definition of amenorrhoea	Bleeding Criteria	Treatment Regime	Intervention	Control
Levens *et al*., (2008)	33-50	22	Symptomatic uterine fibroids > 2 cm in diameter	Menstrual data collected during each of the 3 treatment cycles were scored as 0 if there was no menses and 1 if some menstrual bleeding was present during the cycle. For amenorrheic women, treatment cycles were assigned by 30-day intervals.		3 cycles or 90-102 days if no menses occurred	10 mg or 20 mg UPA	Placebo
Nieman *et al*., (2011)	25-50	42	Symptomatic uterine fibroids > 2 cm in diameter	'No bleeding' reported in daily diary at week 12	'Menorrhagia'	One 12-week treatment course of once daily oral 10 mg or 20 mg UPA or placebo.	10 mg or 20 mg UPA	Placebo
Donnez *et al*., (2012)	18-50	242	At least one symptomatic uterine fibroids 3 - 10 cm in diameter	Pictorial Blood Loss Assessment Chart (PBAC) score = 0	Score of >100 on PBAC during days 1 to 8 of menstruation	One 13-week treatment course of once daily oral 5 mg or 10 mg UPA or placebo.	5 mg or 10 mg UPA	Placebo
Liu *et al*., (2018)	18-50	432	At least one symptomatic fibroid of any size	No bleeding for 35 consecutive days	Menstrual blood loss of 80 ml or greater over the first 8	One 12-week treatment courses of	5 mg or 10 mg UPA	Placebo

			(observable by transvaginal ultrasound)	(spotting permitted) at week 12	days of menstruation during the screening period	once-daily 5 mg or 10 mg UPA or placebo.		
Simon *et al*., (2018)	18-50	157	At least one symptomatic fibroid of any size (observable by transvaginal ultrasound)	No bleeding for 35 consecutive days (spotting permitted) at week 12	Menstrual blood loss of 80 ml or greater measured by the alkaline hematin method over the first 8 days of menses	Two 12-week treatment course of once daily oral 5 mg or 10 mg UPA or placebo	5 mg or 10 mg UPA	Placebo
Irahara *et al*., (2020)	20-50	121	At least one symptomatic uterine fibroids 3-12 cm in diameter	No bleeding for 35 consecutive days at week 12	'Menorrhagia with heavy bleeding for more than 1 day within 8 days from the start of menstruation'	One 12-week treatment course of once daily 2.5mg, 5mg or 10mg UPA or placebo.	2.5 mg, 5 mg or 10 mg UPA	Placebo

Table 2 Proportion of women experiencing adverse events

Paper	**Patients that experienced AEs (%)**			**Women who dropped out of active treatment due to AE (%)**	**Women who dropped out from placebo due to AE (%)**
	5 mg UPA	**10 mg UPA**	**Placebo**		
Levens *et al*., (2008)	-	-	-	-	-
Nieman *et al*., (2011)	-	-	-	4.8	0

Donnez *et al*., (2012)	49.5	53.1	45.8	1.0	2.1
Liu *et al*., (2018)	41.4	46.6	43.2	3.8	5.2
Simon *et al*., (2018)	43.4	54.2	28.6	1.8	0
Irahara *et al*., (2020)	56.5	73.9	80.0	0	0

'-' = Representing no data reported; AE = adverse events; UPA = Ulipristal Acetate

Table 3 Liver Injury Results

Study	**Liver Injury Results**
Levens *et al*., (2008)	Blood was obtained for liver function. 1 case of increased AST/ALT that exceeded 2 times the upper normal range in a patient receiving 20 mg UPA.
Nieman *et al*., 2011	To be eligible, participants required liver function tests within 130% of the upper normal range. LFTs were measured monthly throughout the trial. ALT and/or AST were abnormal in 9 women, all receiving UPA. Placebo vs UPA p= 0.0346.
Donnez *et al*., 2012	No significant difference was found between the groups relating to the incidence of abnormal LFTs. There was no mention of exclusion related to LFTs or any information relating to the occurrence of liver injury.
Liu *et al*., 2018	Participants with ALT, AST, ALP or total bilirubin 2 times the upper limit of normal or greater at screening were excluded. None of the participants were excluded based on the prespecified criteria for hepatotoxicity.

	One severe AE related to abnormal liver function test occurred and was deemed unrelated to treatment.
Simon *et al*., 2018	This study did not provide any information regarding UPAs effects on the liver and did not screen participants liver enzyme levels before/after trial.
Irahara *et al*., 2020	Participants were excluded if evidence of liver dysfunction prior to trial. 1 case of hepatic function disorder and one increase in liver function test in 5 mg group. 1 case of increased GGT in the 10mg group. No severe AEs related to the liver were observed.

AE = Adverse Events; UPA = Ulipristal Acetate; AST = Aspartate Transaminase; GGT = Gamma-Glutamyl Transferase, ALT = Alanine Transaminase, ULN = Upper Limits of Normal; LFT = Liver Function Test

Supplementary Material

Table S1: Inclusion and exclusion criteria

	Inclusion	**Exclusion**
Patient	Symptomatic 1 or more uterine fibroids Age 18-50 years old	Post-menopausal Age < 18 or >50

Intervention	≥ 2 different doses of ulipristal acetate	Surgical
Control	Placebo	Non-placebo
Primary Outcome	Achievement of amenorrhoea	
Secondary Outcome	Safety profile Adverse Events	
Study	Randomised control trial Duration ≥ 12 weeks Number of participants > 20	Duration < 12 weeks Systematic review Number of participants < 20

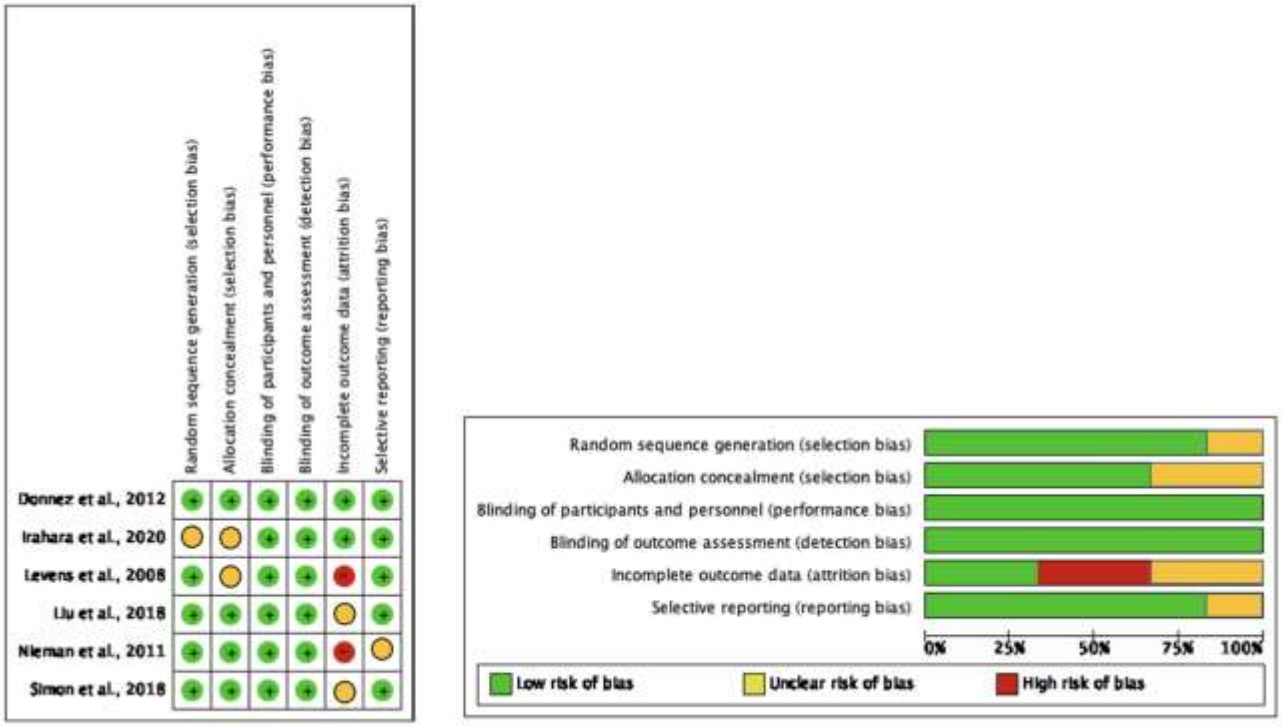

Fig. S1. Risk of Bias Assessment

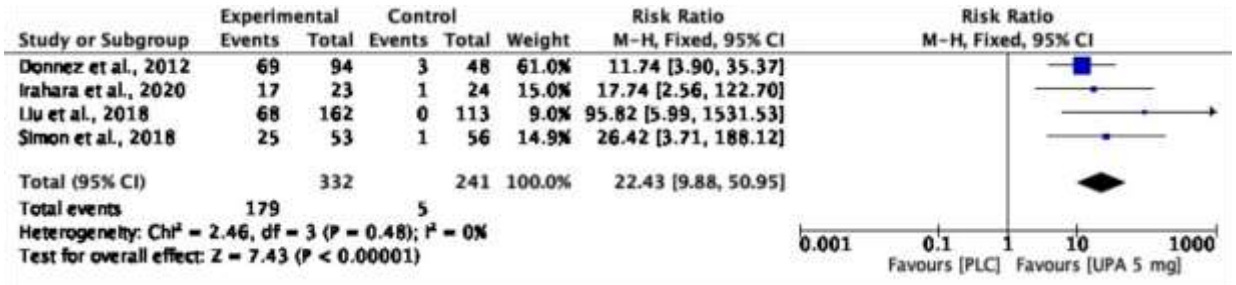

Fig. S2. Forest plot Ulipristal acetate (5 mg) vs. Placebo; Outcome Amenorrhoea

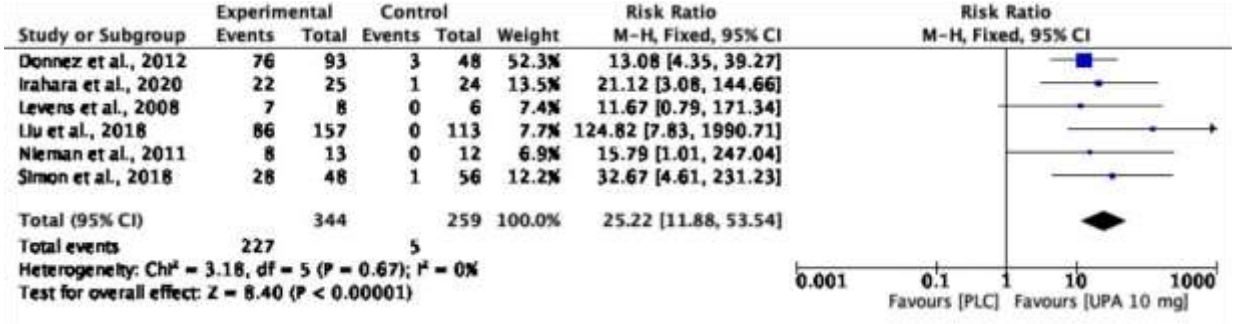

Fig. S3. Forest plot Ulipristal acetate (10 mg) vs. Placebo; Outcome Amenorrhoea