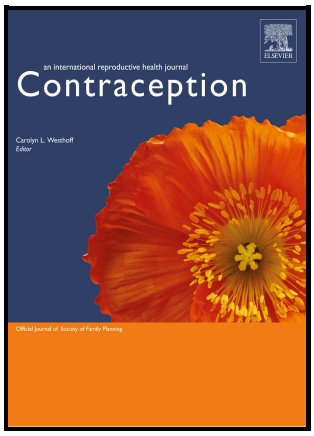
Uses of ulipristal acetate beyond emergency contraception: a narrative review



Ashley M. Ebersole, Abigail Liberty, Alison Edelman, Elizabeth Lyman, Kelly Cleland

PII: S0010-7824(25)00053-8

DOI: https://doi.org/10.1016/j.contraception.2025.110862

Reference: CON110862

To appear in: *Contraception*

Received date: 6 January 2025
Revised date: 25 February 2025
Accepted date: 26 February 2025

Please cite this article as: Ashley M. Ebersole, Abigail Liberty, Alison Edelman, Elizabeth Lyman and Kelly Cleland, Uses of ulipristal acetate beyond emergency contraception: a narrative review, *Contraception,* (2025) doi:https://doi.org/10.1016/j.contraception.2025.110862

Uses of ulipristal acetate beyond emergency contraception: a narrative review

Ashley M. Ebersole, MD, MS[a,b], Abigail Liberty, MD, MSPH[c], Alison Edelman, MD, MPH[d], Elizabeth Lyman, MLIS, AHIP[e] and Kelly Cleland, MPA, MPH[f]

a. Division of Adolescent Medicine, Nationwide Children's Hospital, 380 Butterfly Gardens Drive, Suite LA5E, Columbus, Ohio 43215, USA; Ashley.ebersole@nationwidechildrens.org
b. Department of Pediatrics, The Ohio State University College of Medicine, 700 Children's Drive, Columbus, OH 43205, USA
c. Division of Complex Family Planning, Department of OB/GYN, Oregon Health and Science University, 3181 SW Sam Jackson, UHN 50, Portland, Oregon 97239, USA; liberty@ohsu.edu
d. Division of Complex Family Planning, Department of OB/GYN, Oregon Health and Science University, 3181 SW Sam Jackson, UHN 50, Portland, Oregon 97239, USA; edelmana@ohsu.edu
e. Medical Library, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH, 43205, USA; elizabeth.lyman@nationwidechildrens.org
f. American Society for Emergency Contraception, Lawrenceville, NJ, USA; kelly@americansocietyforec.org

Corresponding author: Ashley M. Ebersole

Word count abstract: 220

Word count text:

- OLD: 3922
- NEW/REVISION: 3949

Abstract

Objectives

Ulipristal acetate (UPA) is a selective progesterone receptor modulator and the most effective oral EC method available in the United States (US). The aim of this review is to identify and describe uses of UPA beyond EC and to further discuss the concerns regarding the possible off-target liver effects.

Study design

We conducted a literature search in August 2024, using Embase, Medline (PubMed), and Cochrane, utilizing a combination of MeSH and keywords for UPA, excluding animal studies, and limiting to English language publications. After excluding duplicates using Covidence, two authors reviewed the remaining 610 results and identified 340 studies. We further excluded case reports and case series.

Results

UPA has shown significant promise for indications outside of EC, most notably treatment of uterine leiomyomas, but also ongoing contraception, prevention and treatment of breast cancer, and abnormal uterine bleeding. While UPA has extensive potential for use both within and beyond reproductive health, unfortunately any ongoing development is at a standstill due to concerns regarding its possible role in causing serious liver injury. The role of

UPA in causing drug-induced liver injury (DILI) is not confirmed and pre-clinical studies during development did not demonstrate a concern that UPA causes DILI.

Conclusions

Access to UPA is crucial not only for EC but for the treatment of many other gynecologic and non-gynecologic conditions.

Keywords:

Contraceptive methods, Emergency contraception, Fibroid, Ulipristal

Abbreviations

DILI: Drug induced liver injury
EMA: European Medicines Agency
ROS: Reactive oxygen species
PAEC: progesterone-receptor-modulator-associated endometrial changes
GBM: Glioblastoma multiforme

1. Introduction

Ulipristal acetate (UPA) is an oral, selective progesterone receptor modulator approved for use as an emergency contraceptive (EC) in Europe in 2009 and the United States (US) in 2010. UPA is the most effective oral EC method available in the US. UPA EC is more effective than levonorgestrel (LNG) EC because it works closer to the time of ovulation, delaying ovulation even after the start of the luteinizing hormone (LH) surge until the LH peak, at which point LNG is no longer effective at inhibiting ovulation[1]. Pregnancy rates following UPA are approximately 2.3% when taken within 120 hours of intercourse[2]. UPA is derived from 19-norprogesterone, which antagonizes the progesterone receptor at the transcriptional level[3].

UPA has shown significant promise for indications outside of EC, most notably treatment of uterine leiomyomas. Emerging evidence suggests the UPA could be effective for ongoing contraception, prevention and treatment of breast cancer, and abnormal uterine bleeding. Unfortunately, regulatory concerns about an extremely rare but serious liver injury have limited further development of UPA for other indications. The aim of this review is to identify and describe uses of UPA beyond EC and to further discuss the concerns regarding the possible off-target liver effects.

2. Materials and methods

We conducted a literature search in August 2024, using Embase, Medline (PubMed), and Cochrane, utilizing a combination of MeSH and keywords for UPA, excluding animal studies and limiting to English language publications. After excluding duplicates through the use of Covidence[4], two of the authors (AME or KC) reviewed the remaining 610 results and identified 340 studies. We further excluded case reports and case series. See Figure 1 for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram and Appendix A for full search strategy. Studies about breast health, cervical preparation and drug induced liver injury (DILI) were manually added after the initial search.

3. Results

3.1 Uterine leiomyomas

Leiomyomas or fibroids are benign tumors of the uterine smooth muscle that can cause abnormal uterine bleeding, pelvic pain, and infertility[5]. Leiomyomas are associated with significant morbidity which may impact quality of life for patients. Current treatment options

for leiomyomas include surgical (e.g. myomectomy and hysterectomy) and non-surgical interventions (e.g. medications and non-surgical radiologic interventions). Hysterectomy is the only definitive treatment, and an individual's desire for future fertility is often a deciding factor in treatment choice.

The majority of the studies identified were related to the use of UPA in the treatment of uterine leiomyomas (n = 228) including six systematic reviews, among which five included a meta-analysis. The studies' main outcomes were control of uterine bleeding or achievement of amenorrhea with use of the medication alone, and the use of UPA pre-operatively to minimize surgical outcomes such as blood loss.

Three of the systematic reviews with meta-analyses assessed achievement of amenorrhea with UPA versus placebo for individuals with uterine leiomyoma[6-8]. Each of the reviews built on the other including the same original studies and then subsequently published studies were added. The reviews consistently found that compared to placebo, UPA had an increased odds of achieving amenorrhea [Kalampokas et al. OR 57.88 (95% CI 19.1, 169.16, Ghonim et al. RR 24.54 (95% CI 10.82, 55.64), Kounidas et al. RR 23.77 (95% CI 11.09, 50.93)]. Kalampokas et al. [8] also reported that the UPA treatment group also had improved quality of life and reduced myoma size compared to the control groups, although a pooled analysis was not available for these outcomes. Ghonim et al. [7] reported on the outcome of heavy menstrual blood loss, UPA groups (RR 12.42, 95% CI 3.38, 45.61) demonstrated improved control. The UPA group also had an improved Uterine Fibroid Symptom and Quality of Life assessment scores with a mean difference -23.18 points (95% CI -29.79, -16.56).

The remaining three reviews assessed use of UPA prior to myomectomy, most commonly UPA 5 mg orally daily for three months (but dosing varied from 5 mg twice a day to intermittent/non-daily dosing) and mostly focused on surgical outcomes and complexities[9-11]. Each of the reviews had differing inclusion criteria. de Milliano et al. [9] included two retrospective cohort studies comparing UPA versus placebo before laparoscopic myomectomy. Shah et al. [10] also focused on laparoscopic myomectomy outcomes and included 13 studies; two of which were also included in the de Milliano review. Vitale et al. [11] in 2020 included four studies that examined the effects of UPA pre-hysteroscopic myomectomy.

The de Milliano et al. and Shah et al. systematic reviews found less blood loss with myomectomy following pre-operative use of UPA (de Milliano et al. weighted mean difference -147 ml, 95% CI -257.52, -37.49, p = 0.009; Shah et al. mean difference -59.85 ml, 95% CI -122.12, -2.42, p = 0.06). de Milliano et al. highlighted one retrospective cohort study that found that the UPA group had a shorter operative time (p<0.001) and less post-operative blood transfusions (p = 0.031)[12]. Shah et al. also found reduced surgical time with pre-operative UPA[10]. Additionally, Shah et al. reported on the change in fibroid size and some other additional patient-oriented outcomes. They found that UPA resulted in a reduction in size of fibroids in 56.5% of users, improved heavy menstrual bleeding in 83%, improved perception of pain in 80.1% and improvement in global symptom scores in 85.2%. Finally, Vitale et al. [11] in 2020 also reported that UPA did not worsen the technical difficulty of the procedure and may increase the chance of complete primary myomectomy in complex procedures.

3.2 Future fertility in individuals with leiomyoma

Future fertility is a challenging outcome to study as this population is already at higher risk for infertility both due to leiomyomas themselves and their treatment (e.g. myomectomy). Additionally, the published literature does not address the ideal timing of conception following UPA alone or as an adjunct and age is an independent risk factor for infertility.

A 2018 systematic review evaluated pregnancy outcomes following UPA treatment for leiomyomas[13]. This systematic review contained six case reports and one retrospective series totaling a cohort of 24 post-UPA pregnancies plus the authors added their own case series that contributed another 47 post-UPA pregnancies for a total of 71 pregnancies. The review did not report an overall denominator of those exposed to UPA who were trying for pregnancy and were unsuccessful or the amount of time from treatment to pregnancy. They found that following the use of UPA, either alone or in conjunction with surgery, conception and favorable pregnancy outcomes occurred. Similarly, a prospective study of 23 pregnant women treated with UPA prior to pregnancy with or without myomectomy, contributed to the favorable course of pregnancy and delivery in women with myomas[14].

3.3 Contraception

UPA has the potential for use as a routine contraceptive method. It causes the inhibition of ciliary beat and muscular contraction of the fallopian tube and down-regulation of genes involved in preparing the endometrium for implantation, resulting in decreased endometrial thickness[15-17]. Using these principles, researchers have investigated UPA's use as a daily, oral contraceptive and a UPA-releasing vaginal ring.

3.3.1 UPA oral pill

A pilot study (N=46) assessed anovulation following UPA 2.5 mg, 5 mg or 10 mg orally daily for 84 days[18]. Similar proportions in the 5 mg (81.8%) and 10 mg (80%) groups experienced anovulation, with no cases of endometrial hyperplasia. A subsequent multi-center phase one - two trial randomized participants to use oral UPA 10 mg or 5 mg orally daily or a three cycle regimen of 5 mg orally for 24 days followed by four placebo days[19]. This study found compatible results to the pilot study with 77% of those in the 10 mg group achieving anovulation in the third month of treatment. Endometrial biopsies during treatment showed progesterone-receptor-modulator-associated endometrial changes (PAEC) in 52 of 164 participants (32%). PAECs are the unique and benign endometrial histology associated with progesterone receptor modulators[20].

3.3.2 UPA-releasing vaginal ring

A randomized control trial (RCT) assessed ovulation inhibition with two different UPA doses of vaginal rings for two consecutive 12-week treatment periods, a low-dose (1.5 mg/day) or a high-dose (2.5 mg/day) UPA[21]. An amendment was made to the study to include treatment with LNG after three cases of heavy or prolonged bleeding occurred with ring use or discontinuation. Therefore, a subgroup of women received LNG 1.5 mg orally twice (at the end of both 12-week ring periods) or once (at the end of the 24-week treatment to reduce endometrial thickening and subsequent heavy bleeding. Ovulation suppression was seen in 81.8% (95% CI 73.3%, 88.5%) of the low-

dose and 86.1% (95% CI 78.1%, 92%) of the high-dose ring users. Research is ongoing in the Dominican Republic to further explore the high-dose 2,500 µg/day UPA releasing vaginal ring with varying doses of LNG[22].

3.3.3 Effect on sperm

Sperm are activated by progesterone for capacitation and acrosomal reaction. UPA can significantly inhibit acrosome reaction and hyperactivation of sperm *in vitro*, and can reduce calcium concentration in sperm, thus causing sperm damage ($p<0.05$)[23, 24]. Additionally, certain levels of reactive oxygen species (ROS) are required for sperm capacitation, the acrosome reaction, and sperm–egg fusion[25]. UPA itself could consume ROS, acting as an antioxidant and decreasing sperm quality[26].

3.4 Abnormal uterine bleeding (AUB)

3.4.1 AUB secondary to long-acting reversible contraceptive (LARC) use

3.4.1.1 *Copper IUD releasing UPA*

The copper IUD is not only the most effective form of EC, but it is a highly effective method of long-term contraception[27]. Despite its low failure rate, it requires a timely in-person interaction to be placed for EC and thus it is not highly utilized. If placed, patients may request early removal of the device due to unwanted side effects of heavy menstrual bleeding, However, as UPA helps with heavy bleeding due to leiomyoma, an IUD with copper and UPA may solve this

problem[28]. A single-blinded proof of concept study investigated 29 participants who received a novel copper-IUD releasing low dose UPA (5, 20 or 40 µg intrauterine/day)[29]. Most participants reported a reduction in bleeding from baseline, demonstrating that low doses of UPA prevent the expected copper-induced increase in bleeding. PAEC was dose dependent and ranged from 10-44%, otherwise there were no serious side effects.

3.4.1.2 Treatment for breakthrough bleeding from the contraceptive implant

Breakthrough bleeding from the contraceptive implant is a common reason for patient dissatisfaction and desire for early removal[30]. A single center, double-blind RCT was conducted among adult women who had the implant in place for greater than 90 days and less than three years and reported > one bleeding episode per 24 days. Participants who received UPA 15 mg orally for seven days reported five fewer days of bleeding over a 30-day reference period after treatment compared to those who were randomized to placebo ($p=.002$)[31]. This led to improved patient satisfaction after four weeks of UPA treatment ($p<0.001$). Of note, this study found that serum progesterone levels do not rise to levels where ovulation occurs in users of UPA with the implant, however the study was not powered to assess this question.

3.4.1.3 Treatment for breakthrough bleeding from the LNG-IUD

In a study of women using the 52 mg LNG-IUD prolonged or frequent uterine bleeding for at least one year were randomized to receive UPA 5 mg orally per day for five days or placebo[32]. IUD users in the UPA 5 mg group had a clinical, not statistical, improvement in abnormal uterine bleeding. Similarly, another study evaluated intermittent UPA to reduce bleeding and spotting for new LNG-IUD users[33]. They administered UPA 150 mg orally for three consecutive days for three cycles starting on days 21, 49 and 77 after IUD insertion. While this regimen initially reduced bleeding and spotting (−10.6% [SD −18.7 to −2.5] difference in bleeding and spotting days with UPA compared to placebo after first treatment), by the third round of UPA, bleeding and spotting worsened +9.5% of days [SD 1.4 to 17.7]. Further research is needed to assess efficacy of hormonal contraceptives with concomitant use of UPA.

3.4.2 Treatment of AUB

For patients with heavy menstrual bleeding (HMB), the LNG-IUD is one of the first-line treatments, however the placement procedure involves a pelvic exam and can be painful and anxiety-inducing for some[34]. A non-blinded RCT among women with HMB assessed UPA 5 mg orally daily for 12 weeks versus the LNG-IUD[35]. The authors found no evidence of a difference in quality of life (as measured by the Menorrhagia Multi-Attribute Scale) between the two treatments, but UPA was superior to the LNG-IUD at inducing amenorrhea by 12 months (64% versus 25% respectively, adjusted odds

ratio (aOR) of 7.12, 95% CI 2.29, 22.2). UPA may be a promising option for patients with HMB.

3.5 Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)

An observational study among women with symptomatic fibroids who took UPA 5 mg orally daily for three months demonstrated that 79.7% had improvements in PMS symptoms as measured by scores on a modified Daily Record of Severity of Problems questionnaire[36]. The most notable improvements were in lethargy, tiredness, sense of fatigue and lack of energy. Similarly, research has been conducted on the benefits of UPA for PMDD. A double-blind, randomized, parallel-group clinical trial examined the benefits of UPA 5 mg orally daily for three 28-day cycles as measured by the Daily Record of Severity of Problems questionnaire. The mean improvement in scores after three months of treatment was 41% (SD=18) in the UPA group, compared with 22% (SD=27) in the placebo group. Improvements were particularly noted for the psychological symptoms associated with the disorder, not the physical symptoms.

3.6 Adenomyosis

Multiple studies have assessed the effectiveness of UPA for pelvic pain secondary to adenomyosis with mixed results. One conference abstract reported on a small, retrospective chart review of patients with pelvic pain from endometriosis, adenomyosis or other pelvic pathology. They found that 89% of the 18 patients who reported their pain (not all patients had documentation of their pre-treatment pain) and were treated with UPA 5 mg orally for about three months (the dose varied as it was retrospective) had improvements in pain[37]. One

multicenter RCT assessed UPA 10 mg orally for three months versus placebo for adenomyosis[38, 39]. While AUB and pain improved during the treatment, both symptoms reappeared when UPA was discontinued. Finally, an abstract of UPA use among patients with concurrent adenomyosis and uterine fibroids demonstrated a reduction in bleeding but a worsening of pain which is in conflict to the fibroid literature.[40].

3.7 Endometriosis

The data on UPA in the treatment of endometriosis is limited. One small study mentioned in the adenomyosis section (3.6) included patients with endometriosis as well as adenomyosis. However, that study did not analyze improvement in pain for participants with endometriosis separately from those with adenomyosis[37]. One *in vitro* study looked at proliferation, ROS, and proinflammatory cytokine production by endometriotic cells and endometrial cells from women with histologically proven endometriosis[41]. While some research showed a lack of endometrial cell proliferation in biopsies of patients with myomas, the cells treated with UPA in the endometriosis study exhibited *in vitro* dose-dependent proliferation and ROS production and failed to revert the proinflammatory cytokine excess[42]. It is unclear whether this paradoxical effect would be present *in vivo* as well.

3.8 Cervical preparation

One pilot study evaluated the use of UPA 90mg orally one day before a second trimester abortion procedure, in combination with pre-operative misoprostol, for cervical preparation[43]. In all 15 study participants, abortion procedures were able to be completed as

planned suggesting adequate cervical preparation from this regimen. Cervical exams prior to administration of misoprostol suggest that UPA alone improved cervical consistency and dilation, although the study was not powered to detect change at these endpoints. The dose was well tolerated with only nausea reported as a side effect. The authors express that additional studies with control groups would be needed to evaluate efficacy and noninferiority of this approach.

3.9 Malignancies

3.9.1 Breast health

While estrogen has long been viewed as a risk factor for breast cancer, the role of progesterone has come under increasing attention. Progesterone causes significant proliferative changes in breast architecture which is thought to increase the risk of cancer[44]. Additionally, the BRCA mutation is associated with aberrant progesterone (not estrogen) signaling. Anti-progestins like UPA might mitigate progesterone-induced breast cancer risk.

3.9.11 Breast cancer prevention

A study using human breast tissue xenografted into mice from 23 women with a BRCA1 mutation and 28 women without a BRCA mutation found that administering UPA in the presence of progesterone reversed the high-risk progesterone-induced breast changes[45]. A mouse BRCA model of breast

cancer found that UPA was more effective than telapristone acetate and mifepristone at preventing tumor development and growth[46].

Translational studies administering UPA 5mg orally daily for 12 weeks to human BRCA carriers observed decreased proliferation as measured by Ki67 in eight out of nine study participants who completed breast biopsies before and after UPA treatment[47]. A larger translational study of 26 women at increased familial risk of breast cancer found that a 12 week course of UPA 5mg orally daily induced protective changes in the breast including decreased proliferation measured by Ki67 (4.89% at baseline to 2.41% following treatment in paired specimens), decreased proportion of luminal progenitor cells and reduced tissue stiffness[48]. Finally, Westhoff et al. [49] randomized women without breast cancer or elevated risk of breast cancer to UPA 10 mg orally daily versus combination oral contraceptive (COC) for 84 days. They found that breast epithelial cell proliferation (as measured by measured by Ki67% positivity and background parenchymal enhancement on breast magnetic resonance imaging) was significantly reduced with UPA.

3.9.1.2 Breast cancer treatment

Several studies have evaluated the role of UPA as an adjuvant for people with breast cancer but to date, no human trials exist evaluating the role of UPA in breast cancer treatment.

Two *in vitro* studies examined the effects of UPA on breast cancer models. A conference abstract from 2015 investigated whether UPA at pharmacological concentrations works as a growth inhibitor in high and low (pre- and post-menopausal) hormonal environments[50]. They found that UPA efficiently decreased the estrogen receptor (ER) positive and progesterone receptor (PR) positive breast cancer model growth induced by both premenopausal and postmenopausal hormone levels. Similarly, another *in vitro* study analyzed the contribution of PR isoforms A and B in breast cancer cell proliferation and found that UPA decreased cell proliferation in the presence of PRA.

Animal models, mice with patient-derived breast tumor, have demonstrated a reduction in tumor size by 30% with UPA use due to slowed tumor growth and increased death of tumor cells[51]. In another mouse model of tamoxifen-resistant tumors, UPA increased tumor latency but did not prevent tumorigenesis in mouse models[52].

3.9.2 Glioblastoma multiforme

Low-dose progesterone has been shown to stimulate the growth of Glioblastoma multiforme (GBM), yet high-dose progesterone may have the opposite effect[53]. In one *in vitro* study, UPA was combined with temozolomide and hydroxyurea to test the hypothesis that this combination may reduce the growth of human GBM cells[54]. They found that all three medications reduced human glioma cell proliferation significantly.

However, the triple drug combination showed the greatest reduction in growth. Although preliminary, these results demonstrate UPA's potential benefits for non-reproductive tract malignancies.

3.9.3 Endometrial Cancer

Progesterone therapy is key in the treatment of endometrial cancer; recently, *in vitro* research has been conducted to examine the benefit of UPA for endometrial cancer. UPA inhibits cell viability of endometrial cancer cell lines and patient-derived primary cancer cells. It also has a synergistic anti-tumor effect when combined with the chemotherapeutic agent paclitaxel[55, 56]. Additionally, UPA appears to decrease endometrial cancer cell growth via activation of apoptosis while simultaneously triggering the activation of proinflammatory cytokines[57]. It is possible that this cytokine activation may be suppressed with contaminant use of an estrogen receptor antagonist.

3.10 Medication abortion

A recent study investigated use of UPA 60 mg orally followed by 800 µg of misoprostol for medication abortion up to 63 days (nine weeks) of gestation. [58] The study did not include a control group, nor did it include a comparison group so this combination cannot be directly compared to established medication abortion regimens (mifepristone + misoprostol or misoprostol alone). This is a small study (133 participants) that is not sufficient to make changes to clinical practice but may be of interest in settings where mifepristone, a key component of

the gold-standard medication abortion regimen, is difficult to get. It is important to consider unintended consequences of this work, which could include politically motivated restrictions on UPA EC in some settings at a time when pregnancy prevention is more critical than ever.

4. Discussion

4.1 Regulatory concerns

While UPA has extensive potential for use both within and beyond reproductive health, unfortunately any ongoing development is at a standstill due to concerns regarding its possible role in causing serious liver injury. See Figure 2 for timeline of studies from this review and authorized indications of UPA. UPA was approved by the European Union and Canada to treat symptomatic leiomyomas (5 mg oral, daily for three months) in 2012 and 2013, respectively. In 2017, the European Medicines Agency (EMA) reviewed post marketing cases of serious liver injury or drug-induced liver injury (DILI) possibly associated with UPA and then subsequently revoked authorization of UPA for this indication by request from Gideon Richter in 2024[59, 60]. It is estimated that likely over a million individuals were treated with UPA for fibroids, many of whom were not surgical candidates for treatment. The EMA identified five cases at the time of their review and a 2020 publication reports on nine cases reported to the FDA (it is likely that a portion of these nine cases reported on by the FDA included some of the five identified by the EMA, however total number is unclear)[61]. The role of UPA in causing DILI was not confirmed and pre-clinical studies during development did not demonstrate a concern that UPA causes DILI[61, 62].

DILI is a rare but not uncommon phenomenon with an estimated incidence of 14-19 cases per 100,000[63]. Genotypic susceptibility likely place some individuals at increased risk for DILI (e.g. PTPN 22 gene, drug-specific HLA polymorphisms). For a drug to be identified as causing DILI, all other causes or risk factors for liver disease must be ruled out. In the case of UPA, causation could not be determined. Even if a drug is known to cause DILI, this does not typically mean that the drug is removed from use but changes in doses or monitoring may be required[63]. A key factor in DILI is with drug cessation that the liver injury resolves.

4.2 Limitations

While this review provided a broad overview of the uses of UPA outside of EC, it had several limitations. First, our literature search was limited to only publications with mention of UPA or other versions of the same drug name in the title of the publication so that we only included the most pertinent studies. See the Appendix for our full search strategy. Additionally, our review excluded animal and non-English studies. Other studies that discussed UPA outside of EC may have been excluded.

The benefits of UPA extend beyond EC and include treatment for leiomyomas, AUB, adenomyosis, endometriosis, PMS, PMDD, malignancies and for use in cervical preparation and possibly as a routine form of contraception; with leiomyoma treatment representing the largest portion of this literature. The future of UPA for long-term contraception is uncertain given the risk for PAECs and DILI compared to the safety of other oral contraceptives available. Given the risk for politically motivated restrictions on UPA, future work around UPA for medication abortion should include rigorous, randomized controlled trials with control groups and

comparison of UPA to established medication abortion regimens. Access to UPA is crucial not only for EC but for the treatment of many other gynecologic and non-gynecologic conditions.

Funding

This manuscript was funded by a subgrant to PSI from the Children's Investment Fund Foundation. Funding for this project supported analysis and writing. The funder was not involved in the decision to submit.

Acknowledgements

None

References

1. Brache V, Cochon L, Deniaud M, Croxatto HB. Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens. Contraception. 2013;88(5):611-8.10.1016/j.contraception.2013.05.010
2. Fine P, Mathe H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. Obstet Gynecol. 2010;115(2 Pt 1):257-63.10.1097/AOG.0b013e3181c8e2aa
3. Wagner BL, Pollio G, Giangrande P, Webster JC, Breslin M, Mais DE, et al. The novel progesterone receptor antagonists RTI 3021-012 and RTI 3021-022 exhibit complex glucocorticoid receptor antagonist activities: implications for the development of dissociated antiprogestins. Endocrinology. 1999;140(3):1449-58.10.1210/endo.140.3.6581
4. Innovation VH. Covidence. Melbourne, Australia.
5. Marsh EE, Wegienka G, Williams DR. Uterine Fibroids. JAMA. 2024;331(17):1492-3.10.1001/jama.2024.0447
6. Kounidas G, Kastora SL, Barnott E, Black L, Robinson-Burke T, Gould A, et al. Efficacy of ulipristal acetate in women with fibroid induced menorrhagia: A systematic review and meta-analysis. Journal of Gynecology Obstetrics and Human Reproduction. 2021;50(9).10.1016/j.jogoh.2021.102173
7. Ghonim M, Magdy R, Sabbour M, Ghonim M, Nabhan A. A systematic review and meta-analysis of ulipristal acetate for symptomatic uterine fibroids. International Journal of Gynecology and Obstetrics. 2019;146(2):141-8.10.1002/ijgo.12868
8. Kalampokas T, Kamath M, Boutas I, Kalampokas E. Ulipristal acetate for uterine fibroids: A systematic review and meta-analysis. Gynecological Endocrinology. 2016;32(2):91-6.10.3109/09513590.2015.1106471

9. De Milliano I, Twisk M, Ket JC, Huirne JA, Hehenkamp WJ. Pre-treatment with GnRHa or ulipristal acetate prior to laparoscopic and laparotomic myomectomy: A systematic review and meta-analysis. PLoS ONE. 2017;12(10).10.1371/journal.pone.0186158
10. Shah N, Egbase E, Sideris M, Odejinmi F. What happens after randomised controlled trials? Uterine fibroids and ulipristal acetate: systematic review and meta-analysis of "real-world" data. Archives of Gynecology and Obstetrics. 2021;303(5):1121-30.10.1007/s00404-020-05918-3
11. Vitale SG, Ferrero S, Caruso S, Barra F, Marín-Buck A, Vilos GA, et al. Ulipristal acetate before hysteroscopic myomectomy: A systematic review. Obstetrical and Gynecological Survey. 2020;75(2):127-35.10.1097/OGX.0000000000000764
12. Ferrero S, Alessandri F, Vellone VG, Venturini PL, Leone Roberti Maggiore U. Three-month treatment with ulipristal acetate prior to laparoscopic myomectomy of large uterine myomas: a retrospective study. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2016;205:43-7.10.1016/j.ejogrb.2016.08.021
13. De Gasperis-Brigante C, Singh SS, Vilos G, Kives S, Murji A. Pregnancy Outcomes Following Ulipristal Acetate for Uterine Fibroids: A Systematic Review. Journal of Obstetrics and Gynaecology Canada. 2018;40(8):1066-76.e2.10.1016/j.jogc.2018.05.020
14. Ignatko I, Kuznetsov, Anton S. The course and outcomes of pregnancy in women with uterine fibroids treated with therapy has ulipristal acetate. Journal of Perinatal Medicine. 2017;45:551-2
15. Jiménez Guerrero M, Fava M, Baccaro LF, Caille AM, Cuasnicú PS, Horcajadas JA, et al. Effect of ulipristal acetate on gene expression profile in endometrial cells in culture and in vivo upon post-ovulatory administration in fertile women. European Journal of Contraception and Reproductive Health Care. 2022;27(3):199-207.10.1080/13625187.2021.1975270
16. Stratton P, Levens ED, Hartog B, Piquion J, Wei Q, Merino M, Nieman LK. Endometrial effects of a single early luteal dose of the selective progesterone receptor modulator CDB-2914. Fertility and Sterility. 2010;93(6):2035-41.10.1016/j.fertnstert.2008.12.057
17. Li HW, Liao SB, Yeung WS, Ng EH, O WS, Ho PC. Ulipristal acetate resembles mifepristone in modulating human fallopian tube function. Hum Reprod. 2014;29(10):2156-62.10.1093/humrep/deu210
18. Chabbert-Buffet N, Pintiaux-Kairis A, Bouchard P. Effects of the progesterone receptor modulator VA2914 in a continuous low dose on the hypothalamic-pituitary-ovarian axis and endometrium in normal women: A prospective, randomized, placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism. 2007;92(9):3582-9.10.1210/jc.2006-2816
19. Westhoff CL, Archer DF, Barnhart K, Darney P, Gilliam M, Jensen J, et al. Evaluation of ovulation and safety outcomes in a multi-center randomized trial of three 84 day ulipristal acetate regimens. Contraception. 2022;112:54-60.10.1016/j.contraception.2022.04.002
20. Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol. 2008;21(5):591-8.10.1038/modpathol.2008.19
21. Huang Y, Jensen JT, Brache V, Cochon L, Williams A, Miranda MJ, et al. A randomized study on pharmacodynamic effects of vaginal rings delivering the progesterone receptor modulator ulipristal acetate: research for a novel estrogen-free, method of contraception. Contraception. 2014;90(6):565-74.10.1016/j.contraception.2014.08.006
22. Nct. A Study to Evaluate the Effect of a Contraceptive Vaginal Ring Delivering Ulipristal Acetate Combined With a Single or Repeated Levonorgestrel on Inhibition of Ovulation, Endometrial Changes and Bleeding Patterns in Normal Cycling Women. https://clinicaltrialsgov/show/NCT02451826. 2015
23. Sha W, Chang X, Han Y, Miao H, Yang Y. In vitro effect of ulipristal acetate on human sperm parameters and function. Pakistan journal of pharmaceutical sciences. 2019;32(3):1419-22

24. Ko JK, Huang VW, Li RH, Yeung WS, Ho PC, Chiu PC. An in vitro study of the effect of mifepristone and ulipristal acetate on human sperm functions. Andrology. 2014;2(6):868-74.10.1111/j.2047-2927.2014.00261.x
25. Sengupta P, Pinggera GM, Calogero AE, Agarwal A. Oxidative stress affects sperm health and fertility-Time to apply facts learned at the bench to help the patient: Lessons for busy clinicians. Reprod Med Biol. 2024;23(1):e12598.10.1002/rmb2.12598
26. Munuce MJ, Cicaré J, Zumoffen C, Caille A, Ghersevich S, Bahamondes L. Effects of ulipristal acetate on sperm DNA fragmentation during in vitro incubation. European Journal of Contraception and Reproductive Health Care. 2013;18(5):355-63.10.3109/13625187.2013.813930
27. Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(5):397-404.10.1016/j.contraception.2011.01.021
28. Bateson D, Harvey C, Trinh L, Stewart M, Black KI. User characteristics, experiences and continuation rates of copper intrauterine device use in a cohort of Australian women. Aust N Z J Obstet Gynaecol. 2016;56(6):655-61.10.1111/ajo.12534
29. Brache V, Vieira CS, Plagianos M, Lansiaux M, Merkatz R, Sussman H, et al. Pharmacodynamics and pharmacokinetics of a copper intrauterine contraceptive system releasing ulipristal acetate: A randomized proof-of-concept study. Contraception. 2021;104(4):327-36.10.1016/j.contraception.2021.06.010
30. Berlan E, Mizraji K, Bonny AE. Twelve-month discontinuation of etonogestrel implant in an outpatient pediatric setting. Contraception. 2016;94(1):81-6.10.1016/j.contraception.2016.02.030
31. Zigler RE, Madden T, Ashby C, Wan L, McNicholas C. Ulipristal acetate for unscheduled bleeding in etonogestrel implant users a randomized controlled trial. Obstetrics and Gynecology. 2018;132(4):888-94.10.1097/AOG.0000000000002810
32. Fava M, Peloggia A, Baccaro LF, Castro S, Carvalho N, Bahamondes L. A randomized controlled pilot study of ulipristal acetate for abnormal bleeding among women using the 52-mg levonorgestrel intrauterine system. International Journal of Gynecology and Obstetrics. 2020;149(1):10-5.10.1002/ijgo.13068
33. Warner P, Guttinger A, Glasier AF, Lee RJ, Nickerson S, Brenner RM, Critchley HO. Randomized placebo-controlled trial of CDB-2914 in new users of a levonorgestrel-releasing intrauterine system shows only short-lived amelioration of unscheduled bleeding. Hum Reprod. 2010;25(2):345-53.10.1093/humrep/dep377
34. Creinin MD, Barnhart KT, Gawron LM, Eisenberg D, Mabey RG, Jr., Jensen JT. Heavy Menstrual Bleeding Treatment With a Levonorgestrel 52-mg Intrauterine Device. Obstet Gynecol. 2023;141(5):971-8.10.1097/AOG.0000000000005137
35. Whitaker LHR, Middleton LJ, Daniels JP, Williams ARW, Priest L, Odedra S, et al. Ulipristal acetate versus levonorgestrel-releasing intrauterine system for heavy menstrual bleeding (UCON): a randomised controlled phase III trial. eClinicalMedicine. 2023;60:101995.10.1016/j.eclinm.2023.101995
36. Chen BF, Powell MC, O'Beirne C. An observation study of the clinical evaluation of symptom relief and side effects associated with taking ulipristal acetate (esmya) including its effect on pre-menstrual syndrome. J Obstet Gynaecol. 2017;37(5):645-8.10.1080/01443615.2017.1287687
37. Scattolon SA, Bullen A, Leyland NA. Ulipristal acetate and pelvic pain. Journal of Minimally Invasive Gynecology. 2017;24(7):S186
38. Fernandez H, Brun JL, Legendre G, Koskas M, Merviel P, Capmas P. Ulipristal Acetate for Adenomyosis: a Multicenter Randomized Trial. Journal of minimally invasive gynecology Conference: AAGL 2019: global congress on MIGS Canada. 2019;26(7):S134
39. Capmas P, Brun JL, Legendre G, Koskas M, Merviel P, Fernandez H. Ulipristal acetate use in adenomyosis: A randomized controlled trial. Journal of Gynecology Obstetrics and Human Reproduction. 2021;50(1).10.1016/j.jogoh.2020.101978

40. Ferrero S, Scala C, Racca A, Tafi E, Venturini P, Leone Roberti Maggiore U. Changes in adenomyosis after treatment with ulipristal acetate. Fertility and Sterility. 2016;106(3):e281-e2.10.1016/j.fertnstert.2016.07.809
41. Reis FM, Chouzenoux S, Bourdon M, Jeljeli M, Chapron C, Batteux F. Effects of Ulipristal Acetate on Reactive Oxygen Species and Proinflammatory Cytokine Release by Epithelial and Stromal Cells from Human Endometrium and Endometriosis. Reproductive Sciences. 2024;31(1):260-6.10.1007/s43032-023-01341-6
42. Whitaker LH, Murray AA, Matthews R, Shaw G, Williams AR, Saunders PT, Critchley HO. Selective progesterone receptor modulator (SPRM) ulipristal acetate (UPA) and its effects on the human endometrium. Hum Reprod. 2017;32(3):531-43.10.1093/humrep/dew359
43. Peterson SF, Lerma K, Shaw KA, Blumenthal PD. Cervical Preparation Using Ulipristal Acetate With Adjunct Misoprostol in Second-Trimester Surgical Abortions. Obstet Gynecol. 2022;139(5):907-9.10.1097/AOG.0000000000004754
44. Soderqvist G, Isaksson E, von Schoultz B, Carlstrom K, Tani E, Skoog L. Proliferation of breast epithelial cells in healthy women during the menstrual cycle. Am J Obstet Gynecol. 1997;176(1 Pt 1):123-8.10.1016/s0002-9378(97)80024-5
45. Communal L, Vilasco M, Hugon-Rodin J, Courtin A, Mourra N, Lahlou N, et al. Proliferation and ovarian hormone signaling are impaired in normal breast tissues from women with BRCA1 mutations: benefit of a progesterone receptor modulator treatment as a breast cancer preventive strategy in women with inherited BRCA1 mutations. Oncotarget. 2016;7(29):45317-30.10.18632/oncotarget.9638
46. Lee O, Bosland MC, Wang M, Shidfar A, Hosseini O, Xuei X, et al. Selective progesterone receptor blockade prevents BRCA1-associated mouse mammary tumors through modulation of epithelial and stromal genes. Cancer Lett. 2021;520:255-66.10.1016/j.canlet.2021.07.034
47. Bartlett TE, Evans I, Jones A, Barrett JE, Haran S, Reisel D, et al. Antiprogestins reduce epigenetic field cancerization in breast tissue of young healthy women. Genome Med. 2022;14(1):64.10.1186/s13073-022-01063-5
48. Howell; D Gareth Evans; Michael Sherratt; Andrew Gilmore; Elaine Harkness; Walid Khaled; Alecia-Jane Twigger; Matt Roberts; Robert Clarke; Bruno Simoes SHAGRPSAACMATMSAAMYLHBFIA, editor **Abstract P1-10-01: Results from the breast cancer - anti progestin prevention study 1 (BC-APPS1) trial - a novel approach in breast cancer prevention** San Antonio Breast Cancer Symposium; 2021; San Antonio: American Association for Cancer Research.
49. Westhoff CL, Guo H, Wang Z, Hibshoosh H, Polaneczky M, Pike MC, Ha R. The progesterone-receptor modulator, ulipristal acetate, drastically lowers breast cell proliferation. Breast Cancer Res Treat. 2022;192(2):321-9.10.1007/s10549-021-06503-1
50. Lee O, Choi MR, Clare SE, Khan SA. Low dose of CDB-2914 and CDB-4124 efficiently inhibit the growth of T47D spheroid induced by pre-menopausal and post-menopausal concentrations of estrogen and progesterone. Cancer Research. 2015;75(9).10.1158/1538-7445.SABCS14-P6-07-07
51. Esber N, Cherbonnier C, Resche-Rigon M, Hamze A, Alami M, Fagart J, et al. Anti-Tumoral Effects of Anti-Progestins in a Patient-Derived Breast Cancer Xenograft Model. Horm Cancer. 2016;7(2):137-47.10.1007/s12672-016-0255-4
52. Lee O, Wang M, Hosseini O, Bosland MC, Muzzio M, Helenowski I, Khan SA. Z-Endoxifen prevents aggressive mammary cancers in mice by inhibiting cell proliferation and creating a tumor suppressive microenvironment. Biomed Pharmacother. 2023;162:114607.10.1016/j.biopha.2023.114607
53. Altinoz MA, Ozpinar A, Elmaci I. Reproductive epidemiology of glial tumors may reveal novel treatments: high-dose progestins or progesterone antagonists as endocrino-immune modifiers against glioma. Neurosurg Rev. 2019;42(2):351-69.10.1007/s10143-018-0953-1

54. Altinoz MA, Yilmaz A, Taghizadehghalehjoughi A, Genc S, Yeni Y, Gecili I, Hacimuftuoglu A. Ulipristal-temozolomide-hydroxyurea combination for glioblastoma: in-vitro studies. Journal of Neurosurgical Sciences. 2024;68(4):468-81.10.23736/S0390-5616.22.05718-6
55. Lee HY, Ko AR, Kang DW, Kim YS, Kim SM, Kang TW, et al. Anti-tumor effect of selective progesterone receptor modulator (ulipristal acetate) on endometrial cancer cell lines. Cancer Research. 2016;76(14).10.1158/1538-7445.AM2016-1191
56. Kanda R, Hiraike O, Hiraike H, Miyagawa Y, Fukui S, Nagasaka K, et al. Ulipristal acetate induces apoptosis and senescence via activation of oncostatin M in endometrial cancer cells. Journal of Obstetrics and Gynaecology Research. 2020;46(8):1543.10.1111/jog.14342
57. Kanda R, Miyagawa Y, Wada-Hiraike O, Hiraike H, Nagasaka K, Ryo E, et al. Ulipristal acetate simultaneously provokes antiproliferative and proinflammatory responses in endometrial cancer cells. Heliyon. 2022;8(1):e08696.10.1016/j.heliyon.2021.e08696
58. Winikoff B, Bousieguez M, Salmeron J, Robles-Rivera K, Hernandez-Salazar S, Martinez-Huitron A, et al. A Proof-of-Concept Study of Ulipristal Acetate for Early Medication Abortion. NEJM Evid. 2025;4(2):EVIDoa2400209.10.1056/EVIDoa2400209
59. Esmya (ulipristal acetate): Withdrawal of the marketing authorisation in the European Union [press release]. Netherlands, 13 September 2024 2024.
60. Agency EM. **Ulipristal acetate 5mg medicinal products - referral**. 2020 13 November 2020.https://www.ema.europa.eu/en/medicines/human/referrals/ulipristal-acetate-5mg-medicinal-products
61. Kang S, Brinker A, Jones SC, Dimick-Santos L, Avigan MI. An Evaluation of Postmarketing Reports of Serious Idiosyncratic Liver Injury Associated with Ulipristal Acetate for the Treatment of Uterine Fibroids. Drug Saf. 2020;43(12):1267-76.10.1007/s40264-020-00960-1
62. Donnez J, Arriagada P, Marciniak M, Larrey D. Liver safety parameters of ulipristal acetate for the treatment of uterine fibroids: a comprehensive review of the clinical development program. Expert Opin Drug Saf. 2018;17(12):1225-32.10.1080/14740338.2018.1550070
63. Fontana RJ, Bjornsson ES, Reddy R, Andrade RJ. The Evolving Profile of Idiosyncratic Drug-Induced Liver Injury. Clin Gastroenterol Hepatol. 2023;21(8):2088-99.10.1016/j.cgh.2022.12.040

Figure captions

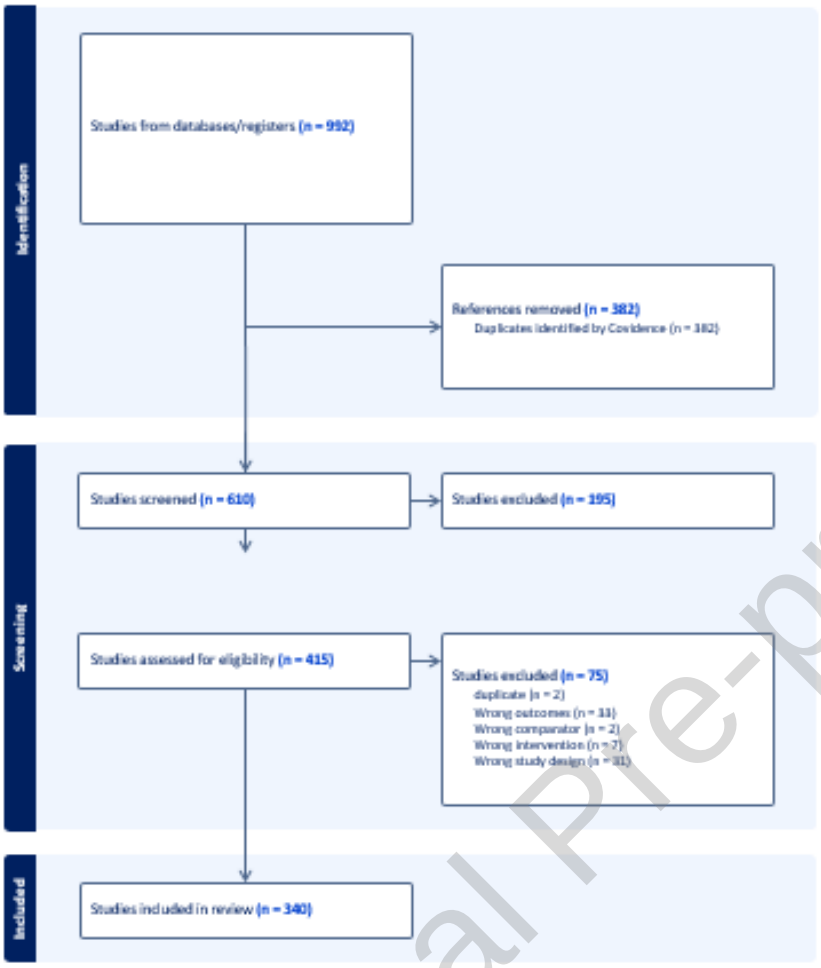


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram of included studies in ulipristal acetate (UPA) review. We conducted a literature search in August 2024, using Embase, Medline (PubMed), and Cochrane, utilizing a combination of MeSH and keywords for UPA, excluding animal studies, and limiting to English language publications. After excluding duplicates using Covidence, two authors reviewed the remaining 610 results and identified 340 studies. We further excluded case reports and case series.

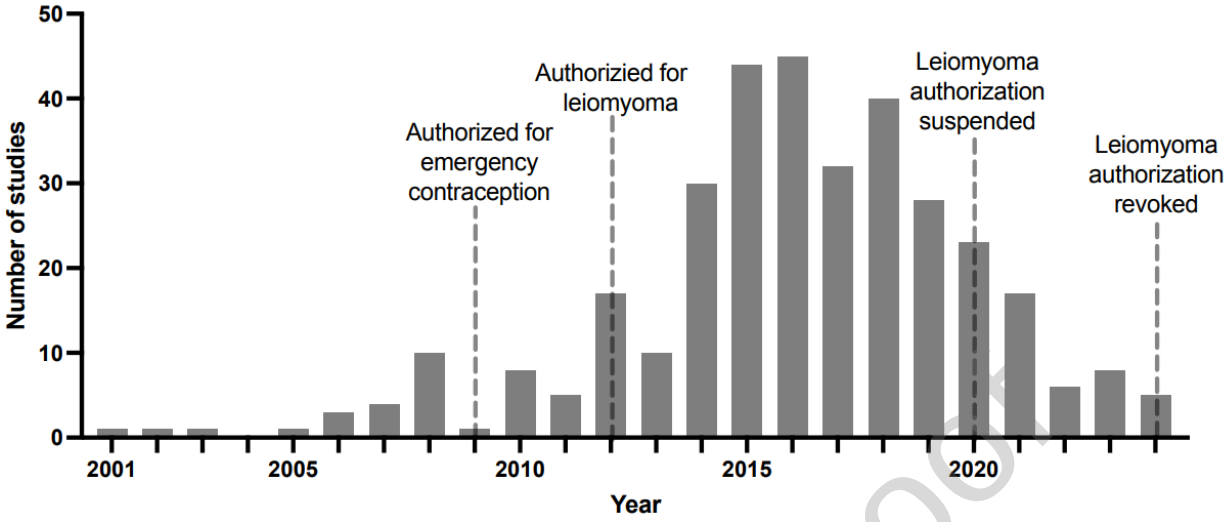


Figure 2: Timeline of studies and authorized indications of ulipristal acetate (UPA). The number of studies by year and key events in UPA licensure. UPA was first licensed for emergency contraception in 2009 in the European Union, 2010 in the USA and 2015 in Canada. UPA was licensed for treatment of leiomyoma in 2012 in the European Union and in 2013 in Canada, but this indication was suspended in both countries in 2020 and revoked in the European Union in 2024 due to regulatory concerns for rare liver toxicity in post-marketing studies.