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Uses of ulipristal acetate beyond emergency contraception

Background

Ulipristal acetate (UPA) is in a class of drugs called selective progesterone receptor modulators (SPRMs). SPRMs are not hormones, but compounds that act on a hormone (progesterone) receptor. Depending on the body tissue, SPRMs may act positively (agonize) or negatively (antagonize) on the progesterone receptor. SPRMs can affect ovulation and the endometrium and thus can potentially be used to treat a number of reproductive health conditions.

UPA is best known as the most effective oral emergency contraceptive (EC) method that is widely available. UPA EC (30 mg) 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]. Emerging evidence suggests the UPA could be an effective treatment for uterine fibroids, ongoing contraception, prevention and treatment of breast cancer, and abnormal uterine bleeding. Some of these conditions, which can significantly affect the health, well-being, and capacity to equally participate in society of women and pregnancy-capable people, have been historically neglected in research and healthcare. This fact sheet explores potential uses of UPA beyond EC.

Methods

We conducted a literature search through August 2024 through Embase, Medline (PubMed), and Cochrane, using a combination of Medical Subject Headings (MeSH) and keywords for UPA. We excluded animal studies, case reports, and case series and limited the search to English language publications. After excluding duplicates, we reviewed 610 results and identified 340 studies.

Emerging and potential uses for UPA

Uterine Conditions

By far, most of the available evidence about uses of UPA outside of EC is for treatment of conditions related to painful uterine growths and excessive bleeding.

→ **Fibroids:** Fibroids, also called myomas or leiomyomas, are benign tumors of the uterine smooth muscle that are associated with infertility, pelvic pain and abnormal uterine bleeding [2]. Current treatment options for fibroids include traditional surgical (myomectomy and hysterectomy), minimally invasive surgical (uterine artery embolization, focused ultrasound surgery and endometrial ablation) and non-surgical interventions (estrogen-progestin contraceptives, levonorgestrel intrauterine devices (IUD), tranexamic acid, other high-dose oral progestins, gonadotropin-releasing hormone analogs); hysterectomy is the only definitive treatment. Recent research has identified progesterone in the development of fibroids, increasing interest in SPRMs for fibroid treatment [3]. In multiple systematic reviews and meta-analyses, UPA significantly achieved amenorrhea (no bleeding or periods), reduced blood loss, and improved quality of life in women with fibroids [4-10].

→ **Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD):** Among women with fibroids and PMS, UPA has been shown to improve lethargy, sense of fatigue and lack of energy [11]. For patients with PMDD and without known fibroids, UPA use may improve the psychological symptoms of the disorder [12].

→ **Adenomyosis:** Adenomyosis is a condition in which the uterine lining grows into the muscular wall of the uterus, enlarging the uterus and often leading to very heavy menstrual bleeding and pain. Multiple studies have assessed the effectiveness of UPA for pelvic pain in patients with adenomyosis and the results are mixed. While it has been found to improve pain, this may be temporary [13-15]. Among those with fibroids and adenomyosis, UPA may improve bleeding, but worsen pain [16]. Further research may help providers understand the benefits of using UPA for patients with adenomyosis.

→ **Infertility:** Fibroids can contribute to infertility through structural uterine changes and UPA may be used to reduce myoma size before pregnancy. UPA has been shown to restore the physiologic shape of the uterus and help patients avoid surgery prior to in vitro fertilization and achieve a pregnancy rate similar to that of patients without fibroids [17, 18]. A systematic review found that UPA, either alone or in conjunction with surgery, can facilitate conception and favorable pregnancy outcomes [19]. Similarly, a prospective study demonstrated that treatment with UPA with or without myomectomy (surgery to remove fibroids) contributed to the favorable course of pregnancy and delivery in women with fibroids [20].

→ **Heavy Menstrual Bleeding:** For those who have heavy menstrual bleeding, UPA alone (three 12-week treatment cycles of 5 mg UPA daily, separated by 4-week treatment-free intervals) was found to be superior to the levonorgestrel IUD at inducing amenorrhea in study participants [21]. UPA may be a promising option for patients with heavy menstrual bleeding who do not want to undergo a procedure.

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1 In 2012, a fibroid medication called Esmya (5 mg UPA daily for up to 3 months) was registered and sold in several countries. After reports of rare but very serious liver injury, regulatory agencies suspended then restricted its use (see section below on Drug-Induced Liver Injury).

Ongoing Contraception and Management of Side Effects

UPA shows promise as a regular method of contraception, as well as a treatment for side effects of long-acting contraception.

→ **Ongoing contraception:** Several studies have assessed UPA as ongoing contraception. As ongoing contraception, UPA may inhibit ovulation and also produce endometrial changes [22-24]. While low dose oral UPA (5-10 mg daily) alone does not reliably suppress ovulation (25), contraceptive vaginal rings containing UPA (1.5 mg or 2.5 mg daily) have shown promise in suppressing ovulation [26, 27]. Finally, sperm are activated by progesterone for capacitation and acrosomal reaction, therefore UPA is also of interest in sperm function. UPA has been found to cause sperm damage and prevent sperm capacitation [28-30].

→ **Breakthrough bleeding:** Breakthrough bleeding is unpredictable spotting that may occur with contraceptive use. It is a common reason for patient dissatisfaction and desire for discontinuation. A study of UPA for breakthrough bleeding from the contraceptive implant demonstrated that users of UPA (15 mg daily for 7 days) had fewer days of bleeding and improved satisfaction compared to implant use alone [31]. Another study found a temporary reduction in irregular bleeding associated with the levonorgestrel intrauterine device in users of UPA (150 mg in divided doses over 3 days) [32].

Malignancies

UPA is of interest in cancer treatment for its anti-proliferative properties.

→ **Breast Cancer:** Breast epithelial cells grow in the luteal phase of the menstrual cycle when the progesterone peak occurs [33]; therefore UPA's progesterone modulating properties may have a role in breast cancer treatment. Two in vitro studies have demonstrated that UPA may decrease breast cancer cell growth [33-35]. UPA may also reduce breast cancer risk; pilot breast cancer prevention trials using UPA are underway in the United Kingdom [36].

→ **Endometrial Cancer:** Progesterone therapy is key in the treatment of endometrial cancer, therefore research has been conducted to examine the benefit of UPA in endometrial cancer treatment. UPA has been shown to inhibit viability and decrease the growth of endometrial cancer cells [37-39].

→ **Glioblastoma multiforme (GBM):** GBM is a fast-growing, aggressive brain tumor with a very poor prognosis. Low-dose progesterone has been shown to stimulate the growth of GBM, yet high-dose progesterone may have the opposite effect. An emerging theory considers that because progesterone may affect GBM, UPA may help reduce the growth of GBM cells. One in-vitro study found that UPA combined with chemotherapy medications temozolomide and hydroxyurea reduced glioma cell proliferation [40]. Further research is needed to determine if this is a promising area of treatment.

Other areas of research

→ **Medication abortion:** A recent study investigated use of 60 mg of UPA followed by 800 micrograms (µg) of misoprostol for medication abortion up to 63 days (nine weeks) of gestation [41]. The study did not 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.

→ **Drug-induced Liver Injury (DILI):** While UPA has extensive potential for use both within and beyond reproductive health, ongoing development is on hold due to concerns regarding its possible role in causing serious liver injury. In 2012, a fibroid medication called Esmya (5 mg UPA daily for up to 3 months) was registered and commercialized in several countries including the European Union, Singapore, Malaysia, Hong Kong, and the United Kingdom [42]. After reports of rare but very serious liver injury, regulatory agencies including the European Medicines Agency temporarily suspended Esmya (2020), then recommended restricting its use (2021) to premenopausal women for whom surgery is not appropriate or has not worked [43]. 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 [44, 45]. Nonetheless, in 2024 companies marketing Esmya in Europe, the United Kingdom, Singapore, Hong Kong, the Philippines and other countries withdrew it from the market. Esmya and generics may still be registered or available in Colombia, Mexico, Russia and other countries.

Summary

Access to UPA EC is crucial as restrictions on abortion in countries such as the United States dramatically raise the stakes for pregnancy prevention. The potential benefits of UPA extend beyond EC and include treatment for fibroids and related pain and infertility, adenomyosis, and heavy menstrual bleeding. UPA may also be a promising option for ongoing contraception and treatment of side effects from long-acting contraception, such as bleeding. Further research is needed to identify the association, if any, between ongoing use of UPA and DILI. Women's health conditions have historically been understudied and research of promising medications, like UPA, for potentially debilitating conditions such as cancer and fibroids should be encouraged.

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