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Review article

Vaginal ring delivery of selective progesterone receptor modulators for contraception

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Abstract

Vaginal ring delivery of selective progesterone receptor modulators (SPRMs) is under development to address the limitations of current hormonal methods that affect use and effectiveness. This method would be appropriate for use in women with contraindications to, or preferences to avoid, estrogens. A contraceptive vaginal ring (CVR) also eliminates the need for daily dosing and therefore might improve the effectiveness of contraception. The principal contraceptive effect of SPRMs is the suppression of ovulation. One limiting factor of chronic SPRM administration is the development of benign endometrial thickening characterized as PRM-associated endometrial changes. Ulipristal acetate (UPA) is approved for use as an emergency contraceptive pill, but no SPRM is approved for regular contraception. The Population Council is developing an ulipristal acetate CVR for regular contraception. The CVR studied is of a matrix design composed of micronized UPA mixed in a silicone rubber matrix The target product is a ring designed for continuous use over 3 months delivering near steady-state drug levels that will suppress ovulation. Results from Phase 1 and 2 studies demonstrate that suppression of ovulation occurs with UPA levels above 6–7 ng/mL.

Keywords: Contraceptive; Vaginal ring; Ulipristal; Progesterone-receptor modulator; Ovulation; Suppression

1. Introduction

About half of all pregnancies in the United States are not intended, and half of these occur as a result of contraceptive failure [1]. While combined hormonal methods like the pill have low failure when used consistently and correctly, the failure rate at 1 year associated with typical use is estimated to be 9% [2]. Furthermore, some women have medical contraindications to the use of estrogen-containing contraceptives [3]. These data suggest that currently available methods do not meet the needs of all couples and support the development of novel methods and delivery systems.

Theoretically, vaginal ring administration of contraception should reduce user errors associated with daily administration and move typical use efficacy closer to perfect use. A combined hormonal contraceptive ring releasing etonogestrel and ethinyl estradiol (EE) is currently approved in the United States and in many countries throughout the world [4], and a Phase 3 clinical trial of a combined hormonal ring containing Nestorone and EE has been completed [5]. A progesterone-releasing vaginal ring has been approved for use in lactating women in Chile, Bolivia, Dominican Republic, Guatemala, Panama and Peru [6].

The development of a bleed-free contraceptive regimen would be highly acceptable to many women [7]. A vaginal ring delivery system with a simplified regimen that did not require removal for a hormone-free interval could potentially improve compliance and contraceptive efficacy. This article reviews the development of a contraceptive vaginal ring releasing ulipristal.

2. Ulipristal

Ulipristal acetate (UPA), also known as CDB/VA-2914, is a selective progesterone receptor modulator (SPRM) developed by the National Institutes of Child Health and Human Development (NICHD) [8]. UPA is a 19-norprogesterone derivative with a 4-*N*,*N*-dimethylaminophenyl in position 11β, with high affinity for the progesterone

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receptor. In receptor binding studies, ulipristal exhibits a relative binding affinity for the progesterone receptor similar to that of progesterone and mifepristone, but a reduced binding affinity for the glucocorticoid receptor as compared with mifepristone [9]. Although UPA is well absorbed orally, pharmacokinetic studies in macaques suggest greater bioavailability with parenteral dosing [10].

UPA has been tested for potential clinical applications in a number of gynecologic applications, including contraception. Observations that a single oral dose of UPA affected maturation and rupture of a pre-ovulatory follicle led to the development of UPA as an emergency contraceptive method [11]. When administered prior to the LH peak, a single oral dose of 30 mg reliably inhibits follicle rupture [12]. UPA is currently approved for use as an emergency contraceptive pill in the European Union and in the United States for use up to 5 days after unprotected intercourse [13]. In addition, when given orally at a daily dose of 5 or 10 mg, ovulation suppression was observed in about 80% of subjects and amenorrhea was seen in 81% and 90%, respectively [14].

These favorable properties supported the investigation of low-dose ulipristal delivery through a vaginal ring for regular contraception.

3. SPRMs for regular contraception

Selective progesterone receptor modulators have been investigated for their potential as novel estrogen-free contraceptives for ongoing use. Since many woman cannot, or prefer not to, use estrogen-containing contraceptives, a highly effect reversible option would fill an important niche [3]. High rates of amenorrhea associated with continuous administration of low-dose antiprogestins suggest that the method could be developed as a "bleed-free" regimen. Daily use of low-dose oral mifepristone suppresses ovulation and has been shown to have a favorable bleeding pattern. In a randomized study comparing 5 mg of mifepristone to a standard 0.3 mg levonorgestrel progestin-only pill, 49% of subjects reported amenorrhea with the SPRM and only 4% bled or spotted for more than 5 days, compared to 0% amenorrhea and 39% with bleeding/spotting using levonorgestrel [15].

Chronic daily use of a SPRM for regular contraception presents different physiologic challenges than use of estrogen-progestin hormonal contraceptives. One potential adverse interaction is non-target binding to the cortisol receptor. This antiglucocorticoid effect varies between the different SPRMs, but is not clinically important with single-dose or short-term treatments even with mifepristone, another SPRM [16]. Longer term studies of high-dose mifepristone (200 mg) for meningioma have not revealed clinically significant changes either, although the diagnosis of hypoadrenalism is difficult because serum cortisol levels are normal or even increased due to this blockade [17]. Hypoadrenalism has not been observed with low-dose mifepristone in contraceptive studies [15].

Since progesterone signaling is required to terminate estrogen-induced endometrial proliferation, chronic administration of a progesterone receptor antagonist could result in endometrial hyperplasia or cancer. Current research suggests that the endometrial effect of a SPRM may be difficult to predict and is dose- and drug-dependent. In women and nonhuman primates, many SPRMs suppress estrogen-dependent mitotic activity in the endometrial glands and block the progestational development of the endometrium, an effect thought to be mediated through the androgen receptor [18]. Macaques fitted with ulipristal acetate intrauterine devices exhibited endometrial atrophy with some glandular cysts [19].

In humans, chronic use of low-dose mifepristone and other SPRMs is associated with endometrial thickening. In the contraceptive study cited above [15], progressive endometrial thickening occurred only in the mifepristone group. The mean endometrial thickness by transvaginal ultrasound in mifepristone subjects was 10.3 mm at 24 weeks compared to 4.0 mm in the levonorgestrel group ($p<.001$). In this study, about a quarter of the mifepristone group underwent a safety endometrial biopsy triggered by a thickness that exceeded 12 mm. The most common (58%) pathologic diagnosis was cystic glandular dilatation of the endometrium. No samples showed hyperplasia or atypia [15]. In a cohort of 16 women with meningioma treated with a much higher dose of mifepristone (200 mg daily) for 1–13 years, endometrial changes described as hyperplasia developed in one premenopausal and one postmenopausal woman and another two women had endometrial thickening without hyperplasia [17]. There were no other abnormalities in liver or renal function or in any other biochemical or hematological parameters associated with this chronic exposure.

4. Ulipristal acetate contraceptive vaginal ring

Vaginal ring drug delivery systems have many advantages. First, drug delivery occurs with steady-state release, so side effects associated with peaks and troughs due to oral dosing are avoided. The ring also provides drug delivery for many weeks, avoiding the need for daily compliance with a pill. Rings capable of delivering drug at a therapeutic level for several months further reduce the chance of user failure. Unlike intrauterine devices or implants, a vaginal ring is entirely woman controlled (e.g., insertion and removal of the ring are performed by the woman).

A low-dose ulipristal contraceptive vaginal ring (CVR) delivery system is under development for regular contraception by the Population Council. The ring is designed to be worn continuously for 3 months. Continuous use should lead to improved compliance over a daily method, and replacement at intervals longer than 1 month would be an improvement over existing one-cycle rings and weekly patches.

The Population Council UPA CVR is composed of micronized UPA mixed in a silicone rubber matrix. An