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Vaginal ring delivery of selective progesterone receptor modulators for contraception

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Abstract

Vaginal ring delivery of selective progesterone receptor modulators (SPRMs) are under development to address 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 principle 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 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 1–2 studies demonstrate that suppression of ovulation occurs with UPA levels above 6–7 ng/mL.

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. While combined hormonal methods like the pill have low failure when used consistently and correctly, the failure rate at one year associated with typical use is estimated to be 9%. Furthermore, some women have medical contraindications to the use of estrogen-containing contraceptives. 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 and a Phase 3 clinical trial of a combined hormonal ring containing Nestorone and EE has been

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completed. A progesterone-releasing vaginal ring has been approved for use in lactating women in Chile, Bolivia, Dominican Republic, Guatemala, Panama, and Peru.

The development of a bleed-free contraceptive regimen would be highly acceptable to many women. 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 paper 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). UPA is a 19-norprogesterone derivative with a 4-N,N-dimethylaminophenyl in position 11 β , with high affinity for the progesterone 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. Although UPA is well-absorbed orally, pharmacokinetic studies in macaques suggest greater bioavailability with parenteral dosing.

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. When administered prior to the LH peak, a single oral dose of 30 mg reliably inhibits follicle rupture. 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. 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.

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 women cannot, or prefer not to, use estrogen-containing contraceptives, a highly effective reversible option would fill an important niche. 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.

Chronic daily use of a SPRM for regular contraception presents different physiologic challenges than 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. Longer term studies of high dose mifepristone (200 mg) for meningioma have also not revealed clinically-significant changes although the diagnosis of hypoadrenalism is difficult because serum cortisol levels are

normal or even increased due to this blockade. Hypoadrenalism has not been observed with low dose mifepristone in contraceptive studies.

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 progestational development of the endometrium, an effect thought to be mediated through the androgen receptor. Macaques fitted with ulipristal acetate intrauterine devices exhibited endometrial atrophy with some glandular cysts.

In humans, chronic use of low dose mifepristone and other SPRMs is associated with endometrial thickening. In the contraceptive study cited above, 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. 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. 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 is 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 one 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 external layer made of a silicone elastomer membrane serves as a rate-limiting barrier, producing a near zero-order delivery rate of UPA. The resulting rings are soft and flexible and donut-shaped, with a core diameter of approximately 57–59 mm and cross-sectional diameter of 6–8 mm depending on the final desired release rate (Fig. 1). Although the cross-sectional diameter of these rings is larger than the current monthly etonogestrel CVR, the silicone elastomer is considerably softer to the touch.

Several early phase clinical trials focusing on the pharmacokinetics and pharmacodynamics of UPA vaginal rings have been completed by the Population Council. In an early Phase 1 study of a CVR releasing 400–500 mcg of UPA per day, serum levels reached a plateau of 2–3 ng/mL within 72 h of ring insertion and stabilized at that level for 30 days, but this level

suppressed ovulation in only 25% (3/12) of women during the 1-month duration of the study suggesting that the dose was too low.

A follow-up open label study of a redesigned CVR releasing 600–800 mcg/day of UPA was recently completed at three study sites (Instituto Chileno de Medicina Reproductiva in Santiago, Chile; USC Los Angeles, CA; and PROFAMILIA, Santo Domingo, Dominican Republic). Healthy women with normal menstrual cycles (aged 21 – 40 years) were followed during a baseline cycle to confirm normal ovulatory function. The CVR was inserted on day 2–5 of the next cycle, and used continuously for 12 weeks. The ring was then removed, and subjects were observed in a post-treatment cycle for return to ovulation. The 12-week treatment interval was divided into three 4-week “treatment cycles” for analysis of the primary outcome of ovulation. This provided five time periods for evaluation: (1) a control cycle (to establish eligibility) prior to ring initiation; (2) Treatment Cycle 1 (weeks 1–4 of ring use); (3) Treatment Cycle 2 (weeks 5–8 of ring use); (4) Treatment Cycle 3 (weeks 9–12 of ring use); and (5) a post-treatment cycle (to establish return to normal menstruation).

Subjects were examined twice weekly (every 3–4 days) to evaluate ovarian function. Blood samples were obtained at all visits to determine estradiol (E2) and progesterone (P) serum concentrations and follicle growth and rupture was monitored by vaginal ultrasound. Serum UPA levels were also obtained. Endometrial biopsies were obtained in the luteal phase of the control cycle, and at the end of the 12-week treatment interval.

Ovarian function during treatment was assessed using a classification system adapted from Hoogland and Skouby [22] that combines morphologic observations (from ultrasound) with hormonal values to categorize the ovarian event as follows: (1) ovulation, (follicular rupture immediately followed by an elevation of serum progesterone (P) concentration that reached 10 nmol/L or more in at least two consecutive samples); (2) ovulatory dysfunction (a follicle 30 mm at rupture and preceded by P levels 10 nmol/L); (3) luteinized unruptured follicle (LUF) (no follicular rupture but more than one P level 5 nmol/L); (4) persistent follicle (follicle 15 mm for 7 days without rupture or P increase); (5) no follicular development: no follicle >12 mm; and (6) no follicular resolution (follicle development 10 mm with no resolution (e.g., could not place in one of the other categories) in the 28-day “treatment cycle”).

Luteal activity (P 10 nmol/L in at least two samples) was observed in almost half (49.5%) of the 111 observed treatment cycles, and met the criteria for ovulation in 32% of cycles with adequate ultrasound assessment (Table 1) [21]. Overall, UPA levels were lowest (mean 4.7 ng/mL) in subjects during ovulatory cycles, and highest (7.6 ng/mL) when no follicular development was observed, and considerable variability was observed between study centers (Fig. 2).

End of treatment endometrial biopsies showed no evidence of endometrial hyperplasia, but benign glandular changes, described as PRM-associated endometrial changes (PAEC), were frequently observed (41%) in a background of inactive or weakly proliferative endometrium. Moreover, these benign glandular changes were significantly more common in biopsies from women with no luteal activity in the preceding 60 days (59%) as compared with those who exhibited luteal activity in the same period (25%).

The endometrial changes were in line with those described with other PRMs [23]. In April, 2006, a National Institute of Child Health and Human Development (NICHD) workshop convened a group of pathologists to define the histological appearances of PRM-treated endometrium and to develop new terminology. Overall, a ‘class effect’ was noted designated as PRM-associated endometrial changes (PAEC) [23]. There was no evidence of hyperplasia

or cytological atypia in any of the endometrial biopsies. Expression of proliferation markers Ki67 and PH3 was significantly increased in post-treatment endometrial glandular epithelium compared to baseline, but baseline biopsies were taken during the secretory phase, when proliferative activity is at very low levels.

5. Future directions

Results from these two preliminary studies demonstrate tolerability of a UPA CVR but support a release rate higher than 800 mcg/day will be required for a reliable contraceptive effect. The primary objective of ongoing studies is to determine the optimal dose of a 3-month UPA CVR that will suppress ovulation in over 90% of cycles. Secondary objectives will be to assess endometrial safety and clinical bleeding patterns.

Clinical trials of two new UPA vaginal rings releasing 1500 and 2500 mcg/day are currently in progress. This study will follow the same general methods and outcomes described in the study of the 600–800 mcg CVR study by Brache et al., but subjects will be randomized to the high or low dose ring and followed for 6 months of treatment exposure for longer term safety evaluation. This study design should also provide more information on bleeding patterns and acceptability during long-term use.

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Fig. 1. Design of a prototype contraceptive vaginal ring (CVR) releasing ulipristal acetate (UPA). a. Vaginal ring dimensions. b. Cross-sectional view of the CVR. The outer area contains UPA in a silicone matrix, and the inner core is an inert silicone core. [International patent application number PCT/US2005/024474 to Sitruk-Ware and Tsong, for “Sustained Release Compositions Containing Progesterone Receptor Modulators” filed July 8, 2005]

Fig. 2. Mean UPA levels at each site during the 12 weeks of treatment. Reproduced from Brache et al, 2012 [21] by permission.

Table 1

Ovarian activity classification during “4-week treatment cycles” with an UPA CVR delivering 600–800 µg/day. Classification based on ultrasound and hormonal data UPA serum levels reflect the mean of the mean values obtained during the treatment cycle where the ovarian activity was reported. (data adapted from Brache et al, 2011 [21])

Ovarian Activity	% of subjects	UPA (ng/mL)
Ovulation	32% (25/78)	4.7
Ovulatory dysfunction	1% (1/78)	5.7
LUF 1 9 10 13	13% (10/78)	5.5
Persistent follicle	31% (24/78)	5.6
No follicular resolution	14% (11/78)	4.7
No follicular development >10 mm	9% (7/78)	7.6