human reproduction ORIGINAL ARTICLE *Fertility control*

Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture

V. Brache [1,*], L. Cochon [1], C. Jesam [2], R. Maldonado [2], A.M. Salvatierra [2], D.P. Levy [3], E. Gainer [3], and H.B. Croxatto [4]

[1]PROFAMILIA, Nicolas de Ovando & Calle 16, Santo Domingo 10401, Dominican Republic [2]Instituto Chileno de Medicina Reproductiva, Santiago, Chile [3]HRA Pharma, 75003 Paris, France [4]Laboratorio de Inmunología de la Reproducción, Universidad de Santiago de Chile y Centro para el Desarrollo de Nanociencia y Nanotecnología-CEDENNA, Santiago, Chile

*Correspondence address. Tel: +1-809-681-8357; E-mail: biomedica@codetel.net.do

Submitted on December 9, 2009; resubmitted on May 11, 2010; accepted on May 25, 2010

BACKGROUND: Current methods of hormonal emergency contraception (EC) are ineffective in preventing follicular rupture when administered in the advanced pre-ovulatory phase. This study was designed to determine the capacity of ulipristal acetate (UPA), a selective progesterone receptor modulator developed for EC, to block follicular rupture when administered with a follicle of ≥18 mm.

METHODS: This was a double-blind, crossover, randomized, placebo-controlled study. Thirty-five women contributed with UPA (30 mg, oral) and a placebo cycle. Serial blood sampling for luteinizing hormone (LH), estradiol and progesterone measurements and follicular monitoring by ultrasound were performed before and for 5 days following treatment. Follicular rupture inhibition was assessed in the overall study population and in subgroups of women stratified by when treatment was administered in relation to LH levels (before the onset of the LH surge, after the onset of the surge but before the LH peak or after the LH peak).

RESULTS: Follicular rupture failed to occur for at least 5 days following UPA administration in 20/34 cycles [59%; 95% confidence interval (CI) (40.7–75.4%)], whereas rupture took place in all cycles within 5 days of placebo intake. When UPA was administered before the onset of the LH surge, or after the onset but before the LH peak, follicle rupture had not occurred within 5 days in 8/8 (100%) and 11/14 [78.6%; 95% CI (49.2–95.3)] cycles, respectively. In contrast, when UPA was given after the LH peak, follicle rupture inhibition was only observed in 1/12 [8.3%; 95% CI (0.2–38.5)] cycles.

CONCLUSIONS: This study demonstrates that UPA can significantly delay follicular rupture when given immediately before ovulation. This new generation EC compound could possibly prevent pregnancy when administered in the advanced follicular phase, even if LH levels have already begun to rise, a time when levonorgestrel EC is no longer effective in inhibiting ovulation.

NCT01107093: Comparison of CDB-2914 versus placebo in the prevention of follicular rupture post-LH surge.

Key words: ulipristal acetate / emergency contraception / follicular rupture / LH surge

trast, in the cycles in which the UPA treatment took place on the day of the LH peak, when a significant rise in *P* had already occurred, follicle rupture followed within 24–48 h with the exception of one woman who exhibited a luteinized unruptured follicle.

The present results indicate that follicular rupture delay is mainly mediated by postponement of LH peak. Nonetheless, UPA may also have a direct effect on the dominant follicle by interfering with progesterone receptor regulated pathways that modulate ovulation, as has been demonstrated in mice (Palanisamy *et al.*, 2006).

Stratton *et al.* (2000) showed that a single mid-follicular dose of 10–100 mg of UPA (CDB-2914) administered with a follicle of 14–16 mm, caused a dose-dependent delay in the time interval from treatment to follicular rupture and suppression of E_2. At higher doses, the initial lead follicle often stopped growing and was replaced by a new lead follicle. This phenomenon was not observed in our study, and it may be related to the fact that we administered UPA later in the cycle, with a pre-ovulatory follicle ≥18 mm, instead of 14–16 mm; another possible difference may be the lower dose used in our study.

Existing hormonal emergency contraceptives based on LNG or estrogen–progestogen combinations administered well before the onset of the LH surge exert inhibitory effects on ovulation via shunting of the LH surge, but they do not significantly delay or inhibit follicular rupture when administered in the advanced pre-ovulatory phase (Croxatto *et al.*, 2001; Gemzell-Danielsson and Marions, 2004; Novikova *et al.*, 2007). In two studies, conducted by the same investigators, using the same design and same conditions of treatment (administration when lead follicle has reached 18 mm in diameter), LNG-EC inhibited dominant follicular rupture for 5 days after treatment in only 2/17 (12%) and 5/31 (16%) women, respectively (Croxatto *et al.*, 2004; Massai *et al.*, 2007). The results from these two trials were very similar and, when combined, this resulted in follicle rupture inhibition in 7/48 women (14.6%) of the LNG studied cycles as compared with 20/34 (58.8%) women with UPA. When comparing the proportions of follicular rupture inhibition at 5 days of treatment using a Fisher exact test, the difference between LNG and UPA is significant ($P < 0.0001$).

In summary, this study provides mechanistic evidence to explain how UPA could be more effective in preventing pregnancy than current reference EC methods. It suggests that UPA is able to inhibit or significantly delay follicular rupture for over 5 days if given immediately before ovulation by postponing the LH peak.

Funding

This study was funded by HRA Pharma.

References

Brache V, Croxatto H, Kumar N, Sitruk-Ware R, Cochón L, Schiappacasse V, Sivin I, Muñoz C, Maguire R, Faundes A. Effect of sexual intercourse on the absorption of levonorgestrel after vaginal administration of 0.75 mg in Carraguard gel: a randomized, cross-over, pharmacokinetic study. *Contraception* 2009;**79**:150–154.

Cheng L, Gülmezoglu AM, Piaggio G, Ezcurra E, Van Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev* 2008;**16**:CD001324.

Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M, Rosenberg M, Higgins J. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol* 2006;**108**:1089–1097.

Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, Nagle C, Ortiz ME, Vantman D, Vega M, von Hertzen H. Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature. *Contraception* 2001;**63**:111–121.

Croxatto HB, Fuentealba B, Brache V, Salvatierra AM, Alvarez F, Massai R, Cochon L, Faundes A. Effects of the Yuzpe regimen given during the follicular phase, upon ovarian function. *Contraception* 2002;**65**:121–128.

Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. *Contraception* 2004;**70**:442–450.

Durand M, Cravioto M, Raymond E, Duran-Sanchez O, Cruz-Hinojosa M, Castell-Rodriguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;**64**:227–234.

Fine P, Mathé H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48–120 h after intercourse for emergency contraception. *Obstet Gynecol* 2010;**115**:257–263.

Gemzell-Danielsson K, Marions L. Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception. *Hum Reprod Update* 2004;**10**:341–348.

Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H *et al.* Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. *Lancet* 2010;**375**:555–562.

Brache e Faundes
Autori dello
Statement FIGO

nts were compared
iii) the timing of the
et was documented.

follicle often stopped growing and was replaced by a new lead follicle. This phenomenon was not observed in our study, and it may be related to the fact that we administered UPA later in the cycle, with a pre-ovulatory follicle ≥18 mm, instead of 14–16 mm; another possible difference may be the lower dose used in our study.

Existing hormonal emergency contraceptives based on LNG or estrogen–progestogen combinations administered well before the onset of the LH surge exert inhibitory effects on ovulation via shunting of the LH surge, but they do not significantly delay or inhibit follicular rupture when administered in the advanced pre-ovulatory phase (Croxatto *et al.*, 2001; Gemzell-Danielsson and Marions, 2004; Novikova *et al.*, 2007). In two studies, conducted by the same investigators, using the same design and same conditions of treatment (administration when

qui affermano che nei giorni pre-ovulatori, i più fertili del ciclo, l'ovulazione è inibita nel 14% dei casi

ted domi-
17 (12%)
and 5/31 (16%) women, respectively (Croxatto *et al.*, 2004; Massai *et al.*, 2007). The results from these two trials were very similar and, when combined, this resulted in follicle rupture inhibition in 7/48 women (14.6%) of the LNG studied cycles as compared with 20/34 (58.8%) women with UPA. When comparing the proportions of follicular

act test, the
l).
to explain

Brache e Faundes nello Statement FIGO dicono che "l'inibizione o il ritardo dell'ovulazione è il principale e possibilmente unico meccanismo d'azione"

Science Ginecologiche on ; 18, 2011

Rosenb
emerge
Gyneco
Croxatto
Ortiz I
of hor
of the
Croxatto
Cocho
follicul
Croxatto
Massai
the sta
0.75-m
70:442
Durand M
Castell
action
contra
Fine P, M
taken
Gyneco
Gemzell-
and le
Rebrod