A prospective, randomized, pharmacodynamic study of quick-starting a desogestrel progestin-only pill following ulipristal acetate for emergency contraception

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Submitted on May 29, 2015; resubmitted on July 7, 2015; accepted on August 27, 2015

STUDY QUESTION: Is there a pharmacodynamic interaction between ulipristal acetate (UPA) 30 mg for emergency contraception and a daily progestin-only contraceptive pill, desogestrel (DSG) 0.75 mg, when initiated the next day?

SUMMARY ANSWER: In this study, DSG impaired the ability of UPA to delay ovulation, but UPA had little impact on the onset of contraceptive effects due to DSG.

WHAT IS KNOWN ALREADY: UPA is a progesterone receptor modulator used for emergency contraceptive (EC) at the dose of 30 mg. UPA delays ovulation by at least 5 days when administered in the mid to late follicular phase. In theory, potent progestins could reactivate progesterone signaling that leads to follicle rupture, thereby impacting the effectiveness of UPA as EC. In addition, UPA could alter the onset of the contraceptive effect of progestin-containing contraceptives started immediately after UPA.

STUDY DESIGN, SIZE, DURATION: A single-blind (for observer), placebo-controlled, partial crossover study was conducted in two sites (Dominican Republic (DR) and the Netherlands (NDL)) over 11 months from October 2012 to September 2013. Healthy female volunteers participated in two of the three treatment cycles separated by a washout cycle. Treatment combinations studied were as follows: (i) a single 30 mg dose of UPA followed by 75 µg per day DSG for 20 days, (ii) a single 30 mg dose of UPA followed by 20 days of placebo matching that of DSG (PLB2) or (iii) one tablet of placebo-matching UPA (PLB1) followed by 75 µg per day DSG for 20 days. Participants were randomized to one of the three treatment sequences (UPA + DSG/UPA + PLB2, PLB1 + DSG and UPA + PLB2/PLB1 + DSG) when a lead follicle was ≥ 14 to < 16 mm diameter on transvaginal ultrasound imaging (TVU).

PARTICIPANTS/MATERIAL, SETTING, METHODS: A total of 71 women were included, and 49 were randomized to a first treatment combination of the three period sequences (20 in the DR and 29 in the NDL); 41 of the 49 continued and completed two treatment combinations (20 in the DR and 21 in the NDL).

MAIN RESULTS AND THE ROLE OF CHANCE: Initiating DSG treatment the day after UPA significantly reduced the ovulation delaying effect of UPA (P = 0.0054). While ovulation occurred in only one of the 29 UPA-only cycles (3%) in the first 5 days, it occurred in 13 of the 29 (45%) UPA + DSG cycles.

LIMITATIONS, REASONS FOR CAUTION: This was a small, descriptive, pharmacodynamic study in which some findings differed by study site. Distinguishing between a cystic corpus luteum and a luteinized unruptured follicle (LUF) by TVU was difficult in some cases; however, the investigators reached consensus, when the study was still blinded, regarding ovulation based on hormone levels and careful review of daily TVU images.

WIDER IMPLICATIONS OF THE FINDINGS: Initiating the use of a DSG progestin-only pill (POP) immediately after UPA reduces the ability of UPA to delay ovulation and thus may decrease its efficacy as EC. If starting a DSG POP after using UPA for EC, and possibly any progestin-only method, consideration should be given to delaying for at least 5 days after UPA intake in order to preserve the ovulation delaying effects of UPA.
Introduction

Ulipristal acetate (UPA) is effective as an oral emergency contraceptive (EC) when administered within 120 h of unprotected sexual intercourse or contraception failure (e.g. condom rupture or missed pills) (Creinin et al., 2006; Fine et al., 2010; Glasier et al., 2010). UPA is a selective progesterone receptor modulator (SPRM) that blocks ovarian progesterone signaling (Nallasamy et al., 2013) delaying follicle rupture for at least 5 days, a time period considered sufficient to compromise sperm viability and the capacity to fertilize an oocyte, thus preventing unwanted pregnancy (Gould et al., 1984; Wilcox et al., 1995; Stratton et al., 2000; Brache et al., 2010). In contrast to levonorgestrel EC, UPA is effective in delaying ovulation even if administered in the advanced follicular phase when the mid-cycle rise in luteinizing hormone (LH) has started; however, its capacity to block follicular rupture is decreased if administered when the LH peak has been reached (Brache et al., 2010, 2013). Current family planning guidelines recommend initiating regular hormonal contraception immediately after EC is used (so-called quick-starting) in order to prevent pregnancies arising from further acts of intercourse after EC use (FSRH, 2010; CDC, 2013). A recent trial investigated the effects on ovarian activity of quick-starting a combined hormonal oral contraceptive pill (COC) after intake of the EC dose of UPA or placebo and showed that UPA did not affect the ability of the COC to induce ovarian quiescence. However, the study was not designed to determine whether the COC initiation affected the ability of UPA to delay ovulation (Cameron et al., 2015). The same concern regarding a potential interaction also exists for a progestin-only pill (POP), since the prior use of a SPRM could also impair the contraceptive effects of a POP started immediately after or the POP may interfere with the ability of UPA to delay ovulation after unprotected intercourse has already occurred. A Phase II study in which an anti-progestagen or a placebo was administered intermittently every 28 days to users of desogestrel (DGS)-only pills (75 ug) showed an increase in ovulation rate among the women who received the anti-progestagen compared with placebo (29 versus 0%) (vanHeusen et al., 2000).

Therefore, it is important to understand the potential interactions between UPA and regular oral contraceptives (OCs). This study explores the possible pharmacokinetic (PK) and pharmacodynamic interactions between UPA and a DSG-only pill. The interaction will be characterized by its possible effect on (i) the occurrence of ovulation within the first 5 days following UPA intake (risk related to the unprotected intercourse that motivated EC intake), (ii) the occurrence of ovulation within 21 days after treatment initiation (risk related to further unprotected intercourse taking place in the same cycle after EC intake), (iii) the onset of mucus blockage (if ovulation occurs, mucus can still block the sperm penetration, thereby inhibiting fertilization after unprotected intercourse taking place after EC intake).

Materials and Methods

Study design

This was a prospective, randomized, single-blind (for observer), incomplete crossover study in which each woman completed two of three treatment sequences. Treatment combinations studied were as follows: (i) a single 30 mg dose of UPA (ellaOne®, 30 mg UPA, HRA Pharma, Paris, France) followed the next day by 75 mg per day DSG (Cerazette®, 75 mg DSG, N.V. Organon, the Netherlands) for 20 days, (ii) a single 30 mg dose of UPA followed by 20 days of a placebo-matching DSG (PLB2; prepared by Cenex, France) or (iii) one tablet of placebo-matching UPA (PLB1; prepared by Cenexi) followed by 75 mg per day DSG for 20 days. The study was conducted in the Dominican Republic (DR) (Center 1) and the Netherlands (NDL) (Center 2), with prior ethics committee approval at each site.

Participants

Healthy women, 18–35 years old, with body mass index (BMI) < 30 kg/m² and who had not been using hormonal contraception for at least one complete menstrual cycle, were eligible for enrollment. Women could participate if they were not at risk of pregnancy because they were not sexually active or if active, had been sterilized (tubal ligation) or used condoms and avoided hormonal contraception for the duration of the study. Women were ineligible if their menstrual cycle lasted <24 or >35 days, if they were pregnant or breastfeeding or if they were using an intrauterine device. Women were also excluded if they had had an abnormal cervical smear defined as high grade within the last 11 months, a past history of cancer, any clinically significant laboratory findings at screening or were on chronic treatment with glucocorticoids or taking any medication thought to interact with UPA or DSG per their respective Summary of Products Characteristics. All participants gave written informed consent prior to enrollment.

Primary outcomes

Primary outcome measures for efficacy, corresponding to the two mechanisms of action of the DSG and POP, studied (i) the occurrence of ovulation either within a period of 5 days or within 21 days after treatment initiation, and (ii) the number of days between treatment initiation and effective inhibition by mucus.

Secondary outcomes

Secondary outcome measures for efficacy included hormonal [estradiol (E2), progesterone, LH serum levels] and clinical characteristics of the menstrual cycle under treatment. PK outcome parameters of UPA (and its main metabolite) and etonogestrel (DGS’s main metabolite) were measured in the plasma in order to specifically characterize the effect of DSG intake on the Cmax and AUC for UPA and the effect of prior UPA intake on the PK profile of DSG.

Study procedures

Following inclusion and starting 5 days after onset of menses, participants visited the study center three times a week until the mean diameter of the
dominant follicle (measurement of the two largest perpendicular axes) was \( \geq 12 \text{ mm} \) by transvaginal ultrasound imaging (TVU) and then daily until it was between 14 and 16 mm. Once the lead follicle was \( \geq 14 \text{ mm} \), women were randomized to one of the three treatment sequences stratified by site: UPA + DSG/UPA + PLB2, PLB1 + DSG/UPA + DSG or UPA + PLB2/PLB1 + DSG. Randomization per block of three was performed using a unique list prepared for the study sites with sequentially numbered, coded treatment packages corresponding to the treatment sequence. Tablets were taken in the presence of research staff on Days 1 – 6 of treatment, at approximately the same time. Remaining tablets were given to the women with instructions to take one tablet a day for 15 consecutive days at approximately the same time. Subjects made daily visits to the study site on Days 1 – 6 of treatment for measurement of ovarian follicle size, serum progesterone, LH and E2 levels and assessment of cervical mucus scores. TVU was performed daily until follicle rupture was documented or the follicle was \(< 14 \text{ mm} \) on two consecutive visits, whichever occurred first. Cervical mucus was also assessed daily until a cervical mucus WHO permeability score of \( \leq 4 \) was recorded on two consecutive visits. Visits then continued twice weekly, and mucus sampling was discontinued until the end of the treatment period. Progesterone was measured on all visits, while LH and E2 were measured on daily visits (preceding follicular rupture or before reaching a cervical mucus score of \( \leq 4 \)). After a washout period of one menstrual cycle, participants received the second treatment combination in their sequence according to the same protocol.

Ovulation was defined by both documentation of follicular rupture by TVU and serum progesterone levels \( \geq 10 \text{ nmol/l} \) on two consecutive visits. A persistent follicle was defined as a follicle of \( > 15 \text{ mm} \) for at least 7 days without rupture and without an increase in progesterone (\( < 5 \text{ nmol/l} \)). A luteinized unruptured follicle (LUF) was said to have occurred when progesterone levels were \( > 5 \text{ nmol/l} \) at least two consecutive samples in the absence of follicle rupture. In case of a persistent follicle or LUF of \( > 25 \text{ mm} \) at the end of the second treatment period, weekly TVUs were performed until follicle collapse or until it was \(< 15 \text{ mm} \). As it was difficult in some cases to distinguish by ultrasound between a corpus luteum cyst following ovulation and a LUF, follicular outcome status was reviewed in detail by investigators from both sites (follicular growth dynamics, specific daily ultrasound images and concomitant hormonal levels) at the time of the blind review. When in doubt, a conservative approach of classifying the follicular outcome as ovulation by default was taken. The final outcome for each treatment cycle was agreed upon by formal consensus of the investigators before unblinding.

Hormone concentrations in samples from both sites were measured by a central laboratory (CEMO, Choisy le Roi, France).

Cervical mucus was aspirated using polyethylene tubes and assessed according to methodology described in the World Health Organization (2010). A WHO cervical mucus score is based on volume, consistency (viscosity), ferning, spinnbarkeit and cellularity with each variable scored on a four-point scale (0 – 3). Because volume was not assessable due to our interest in not aspirating the total amount of mucus on each sampling, and thus try to preserve ‘real-life conditions’, where the permeability is the result of several previous days of mucus production, the maximum permeability score on any day was 12 and a conservative definition of effective inhibition of mucus was employed (WHO score \( \leq 4 \)) (Dunson et al., 1998).

**Pharmacokinetics**

To evaluate the effects of treatment combinations on PKs of both drugs, blood sampling was performed before the start of treatment then 1, 2, 5, 24, 48, 72, 96 and 120 h after UPA intake on Day 1 of each treatment period. Plasma UPA and its main metabolite, 11-demethyl UPA, were analyzed at all time points; plasma etonogestrel, the active metabolite of DSG, was analyzed from blood samples taken before and 2 h after intake of the second to sixth treatment tablets (i.e. the first to fifth DSG/PLB2 tablets). Analysis was performed by a central laboratory (Lambda Therapeutic Research, Ahmedabad, India) using a validated LC-MS/MS method.

**Statistics**

For this exploratory study, 50 women were to be enrolled in order to provide sufficient descriptive statistics for each of the treatment combinations. Analyses were performed using all completed treatment cycles.

For time to event analyses, the hazards for ovulation were not proportional and the originally planned analyses (Cox model and log-rank statistics) were insensitive to treatment differences. As the expected effect of UPA is to delay ovulation for \( \sim 5 \) days, a logistic regression model was used to analyze the rate of ovulation occurring within the first 6 days after UPA treatment for the UPA + DSG and UPA + PLB1 combinations using a binary variable (yes/no ovulation). The model used treatment as a fixed factor and subject as a random factor. A comparable model was used for the rate of ovulation in the first 20 days. An order effect was found to be absent (non-significant contribution of period to the model) and was therefore not included in the reported model.

To overcome the problems with an incomplete crossover design, a series of additional tests was performed for testing the difference between treatments. For each treatment comparison, the data were partially paired (both treatments assessed within a subject) and partially non-paired (only one treatment assessed). Treatment effects for paired data were tested with McNemar’s test, and non-paired data were analyzed with a Wilcoxon two-sample test. Results from these specificity tests were highly consistent with the main logistic regression model results and are, for the sake of brevity, not included in this article.

**Results**

A total of 71 subjects were screened; of them, 11 did not meet the inclusion criteria and 11 more failed to meet the protocol requirements for randomization (Fig. 1). A total of 49 women were included, 20 in DR (Santo Domingo) and 29 in NDL (Groningen). All 49 subjects were included in the full analysis set (FAS), per protocol set (PP), PK and safety analysis. There were eight subjects in NDL dropped out between the two treatment periods (the reasons for dropout were varied: hormonal treatment intake, unprotected intercourse, no return of menses, difficulty to comply with study schedule and inadequate follicular growth in the early second treatment cycle) leading to a total of 41 subjects completing both cycles, 20 in DR and 21 in NDL. There were no dropouts in DR. Primary outcome measures were evaluated for each treatment combination, UPA + DSG, PLB1 + DSG and UPA + PLB2, using data collected from all completed 90 treatment cycles (FAS, 49 from the first period and 41 from the second period).

A total of 48 subjects and 87 treatment cycles were used for efficacy analyses (Fig. 1).

**Baseline characteristics**

Randomization resulted in similar demographic characteristics for the three sequences and three treatment combinations studied, although there were notable differences between centers in terms of age and race (Table I). Women in DR were older than those in NDL (30.4 ± 2.5 versus 23.8 ± 4.6) and all were mixed race (white/black), while those in NDL were all Caucasian. Contraceptive practices were also different; women in DR had all undergone surgical sterilization, while none in NDL were sterilized.
Baseline values for cycle and hormonal parameters, dominant follicle size and mucus score on the day of randomization did not differ overall between the treatment combinations (Table II). There was no between-center significant difference for the dominant follicle size nor the mucus score at baseline. Progesterone levels and LH were not clinically significantly different but were statistically significantly higher in the NDL (P = 0.001 and P = 0.023). Estradiol was higher in the DR (P = 0.036, Table II).

**Timing and occurrence of ovulation**

There was a highly significant difference in the proportion of cycles where an ovulation occurred within the first 5 days in the UPA + DSG treatment cycles compared with UPA alone (UPA + PLB2) (P = 0.0054) (Fig. 2). While ovulation occurred in only one of the 29 UPA-only cycles in the first 5 days after UPA alone versus 13 of 29 (45%) in the UPA + DSG cycles. When comparing the proportion of ovulations in women in sequence 1 (13 women who received both treatments), the data are essentially the same (0/13 ovulations within the first 5 days after UPA alone versus 7/13 within the first 5 days after UPA + DSG). The median time to ovulation was 8 days for UPA-only when compared with 4 days for UPA + DSG (Table III). When considering ovulation throughout the entire treatment period, ovulation occurred in 24 of the 29 UPA-only cycles (83%) and in 15 of the 29 UPA + DSG cycles (52%).

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**Table I** Demographics of participants in each group and center.

<table>
<thead>
<tr>
<th>Total women</th>
<th>Treatment UPA + PLB, n = 31 cycles</th>
<th>Treatment UPA + DSG, n = 30 cycles</th>
<th>Treatment PLB + DSG, n = 29 cycles</th>
<th>Center Dominican Republic, n = 20 women</th>
<th>Center The Netherlands, n = 29 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), mean (SD)</td>
<td>26.4 (4.6)</td>
<td>26.8 (5.0)</td>
<td>27.1 (4.5)</td>
<td>26.0 (4.1)</td>
<td>30.4 (2.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White/Caucasian</td>
<td>29 (59.2)</td>
<td>19 (59.4)</td>
<td>16 (53.3)</td>
<td>16 (55.2)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Bi-racial (white/black)</td>
<td>20 (40.8)</td>
<td>13 (40.6)</td>
<td>14 (46.7)</td>
<td>13 (44.8)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>64.8 (9.9)</td>
<td>64.6 (9.7)</td>
<td>66.0 (10.7)</td>
<td>63.4 (9.1)</td>
<td>63.4 (7.9)</td>
</tr>
<tr>
<td>Height (m), mean (SD)</td>
<td>1.67 (0.1)</td>
<td>1.67 (0.1)</td>
<td>1.67 (0.1)</td>
<td>1.65 (0.05)</td>
<td>1.60 (0.1)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>23.3 (3.1)</td>
<td>23.1 (3.2)</td>
<td>23.7 (3.3)</td>
<td>23.2 (2.8)</td>
<td>24.7 (3.0)</td>
</tr>
</tbody>
</table>

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**Figure 1** Consort flow chart showing recruitment and follow-up of subjects. UPA, ulipristal acetate; DSG, desogestrel; PLB, placebo.
Interaction between UPA EC and quick-starting DSG pills

Table II Baseline values for cycle and hormonal parameters per treatment and per center (FAS population).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Treatment Kruskal–Wallis, P-value</th>
<th>Center Kruskal–Wallis, P-value center</th>
<th>Dominant follicle size (mm), median quantile [0.025;0.75]</th>
<th>Mucus score, median quantile [0.025;0.75]</th>
<th>Progesterone (nmol/l), median quantile [0.025;0.75]</th>
<th>Estradiol (pmol/l), median quantile [0.025;0.75]</th>
</tr>
</thead>
</table>

Some differences between the two centers were observed for the UPA + DSG group of treatment. In DR, overall more women ovulated than in NDL [71.4% (10/14) versus 33.3% (5/15), P = 0.0642]. Furthermore, more women ovulated within the first 5 days of treatment initiation in DR than in NDL [71.4% (10/14) versus 20.0% (2/15), P = 0.0169], and the median time to ovulation was also shorter (4 versus 5.5 days) (Table II). These differences were not found for the two other treatment combinations (Table III), or for mucus blockage outcomes or for the PK parameters (data not shown).

In the case of DSG alone (PLB + DSG), ovulation occurred in 11 of the 29 (38%) cycles and in all cases within 5 days of treatment (Fig. 2, Table III). DSG inhibited ovulation during the whole period of treatment in the remaining 62% (18/29) of the cycles, in which the dominant follicle developed into a persistent follicle in 13/29 (45%) cycles or a LUF in 5/29 (17%) of the cycles.

Compared with DSG alone, UPA taken the day before DSG had a small delaying effect on the occurrence of ovulation (median day of ovulation 3 versus 4, Fig. 2, Table III).

Cervical mucus evaluation

Baseline cervical mucus scores were similar in all treatment groups (Table II). On the day of DSG administration, the median cervical mucus score was 8 and 7, for DSG and UPA + DSG, respectively. Since mucus permeability decreases as progesterone levels increase, the cycles in which ovulation occurred prior to mucus blockage were censored and not included in the analysis (DSG n = 8 and UPA + DSG n = 11). Figure 3 shows the day a cervical mucus score of ≤4 was reached after DSG intake (second day of treatment). All mucus scores were poor within 4 days of DSG intake in the PLB + DSG cycles and within 6 days in the UPA + DSG cycles (Fig. 3). Mucus blockage had tendency to occur slightly faster in the DSG treatment group when compared with the UPA + DSG group.

In the DSG cycles, if ovulatory cycles are included, cervical mucus was impermeable by Day 2 after DSG intake in 62% (18/29), by Day 3 in 86% (25/29) and by Day 4 in 100% (29/29). However, since ovulation (when it occurred) occurred shortly after DSG intake, mucus blockage was achieved prior to ovulation in only 3/11 of the DSG ovulatory cycles.

UPA had no effect on cervical mucus. In 19 of the 21 UPA cycles with delayed ovulation in which cervical mucus samples were taken prior to follicle rupture, the cervical mucus score was good (≥10); in none of these cycles was there a poor cervical mucus score.

Pharmacokinetics

There were no differences in Cmax or AUC for UPA or its metabolite 11-demethyl UPA in the UPA + DSG group compared with UPA alone. PK parameters for the active metabolite of DSG, etonogestrel, were also unchanged by a prior administration of UPA.

Discussion

This randomized study of pharmacodynamic and PK interactions between UPA and DSG aimed to clarify whether immediately starting daily DSG after UPA use for EC impacted the capacity of UPA to delay ovulation and if the intake of UPA immediately before the initiation of
a DSG POP had an effect on the contraceptive mechanisms of the POP (inhibition of ovulation and blockage of mucus permeability).

Our results show a potentially important impact of immediately starting the use of a DSG POP on the ability of UPA to delay ovulation. A single dose of 30 mg UPA may indeed block ovarian progesterone receptor (PR) signaling, particularly mediated by PR-A, which interrupts expression of several gene products required for follicle rupture and ovulation (Nallasamy et al., 2013). However, in this study, when daily doses of 75 μg DSG begin the day after taking UPA, DSG appears to be able to reinitiate progesterone signaling and decreases the ovulation delaying effect of UPA. This pharmacodynamic interaction could have consequences for women quick-starting DSG after using EC following unprotected intercourse, increasing the risk of an unplanned pregnancy should ovulation occur in the next 5 days.

This study also showed that prior use of UPA had little impact on the onset of action of DSG and thus its potential contraceptive effect.

The results of this study also confirm that DSG may be initiated near mid-cycle provided that the first few days of use are protected by a barrier method (it takes a maximum of 4 days to obtain impermeable mucus, and ovulation when it occurs, does within the first 5 days). The current recommendations reference a delay of 2 days before the mucus effect can be considered as effective to protect from the risk of pregnancy, but in this study, 38% of the subjects needed ≥2 days of POP use (McCann and Potter, 1994; FSRH, 2010, 2015). However, it should be noted that in this study, DSG was administered at a time when regular or good cervical mucus was already present in almost all cycles.

This study also confirms that after using UPA alone, at a follicular size around 14–16 mm, ovulation is postponed and takes place in a median of 8 days after intake. These results are also consistent with pharmacodynamic studies that have established that a single dose of 30 mg UPA administered in the advanced follicular phase (lead follicle diameter

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**Figure 2** Day of occurrence of ovulation from the day of treatment initiation (efficacy population). UPA, ulipristal acetate; DSG, desogestrel; PLB, placebo.

<table>
<thead>
<tr>
<th>Table III Ovulation frequency and timing per treatment and per center.</th>
<th>UPA + PLB, n = 29</th>
<th>UPA + DSG, n = 29</th>
<th>PLB + DSG, n = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, n = 87 cycles</td>
<td>1 (3.4) (1)</td>
<td>13 (44.8)</td>
<td>11 (37.9) (2)</td>
</tr>
<tr>
<td>Ovulation &lt; Day 6, n (%)</td>
<td>24 (82.8) (3)</td>
<td>15 (51.7)</td>
<td>11 (37.9) (4)</td>
</tr>
<tr>
<td>Day of ovulation, median quantile [0.025; 0.75]</td>
<td>8.0 [5.6–12.6] (5)</td>
<td>4.0 [3.5–8.7]</td>
<td>3.0 [3.0–4.8] (6)</td>
</tr>
</tbody>
</table>

(1–6) Logistic regression model (fixed effect: treatment, random effect: subject) comparing with UPA + DSG: (1) p = 0.0244, (2) p = 0.3360, (3) p = 0.0054 and (4) p = 0.6753.

(β–6) Wilcoxon–Mann–Whitney test; compared with UPA + DSG: (5) p < 0.0001 and (6) p = 0.5485.
18 mm) significantly delays ovulation by a median of 6 days; 100% of the ovulations were postponed by at least 5 days, provided that intake took place before LH had started to rise (Brache et al., 2010). These two pharmacodynamic studies clearly show that ovulation is mainly postponed, not inhibited, and therefore if further acts of unprotected intercourse occur, women will be at risk of pregnancy. Glasier et al. (2011) reported that women who had subsequent unprotected intercourse were greater than four times more likely to get pregnant than those who did not report further intercourse. Because of this known risk, it is essential to protect every further intercourse and initiate regular contraception as soon as possible following EC use.

A recent study in which a COC was initiated after UPA use showed that UPA did not affect the ability of the COC to induce ovarian quiescence; however, the study was not designed to determine whether the COC initiation affected the ability of UPA to delay ovulation (Cameron et al., 2015). DSG was selected for this study as it is much more frequently prescribed than levonorgestrel as POP regular contraceptive in Europe due to its high efficacy and combined ability to reduce mucus permeability and suppress ovulation. Compared with progesterone, DSG has an 8 times higher affinity for PRs (850 versus 100 relative binding affinity compared with progesterone), and this, together with its longer half-life (36 versus 12 h), reduces the risk associated with missed pills (Phillips et al., 1990). These DSG properties may explain the pharmacodynamics interaction described in the current study; any extrapolation to other progestin agents or route of administration can only be tentative.

The limitations of this study are its small size, the complex design chosen to enhance compliance for this very demanding study, the demographic differences between the two study sites and the difficulty in distinguishing follicle rupture with ensuing cystic corpus luteum formation (ovulation) from LUF by TVU.

Another limitation of our protocol was that cervical mucus evaluation was discontinued when a score of \( \leq 4 \) was observed on two consecutive visits. However, if initial measurements were taken when E2 levels were not sufficiently high, mucus scores may have been low, resulting in a score of \( \leq 4 \) on two consecutive visits before a treatment effect on mucus levels could even have been observed. Additionally, mucus permeability scores are decreased by the rise in progesterone following ovulation. Since ovulation occurred shortly after treatment in many cycles, this limited the ability to evaluate accurately the DSG progestin effect.

Several studies have evaluated the effect of starting a progestin-only method at mid-cycle in terms of frequency and timing of ovulation and impermeable cervical mucus following initiation. One study reported that follicle rupture occurred within 24–72 h of levonorgestrel contraceptive implants inserted in the advanced follicular phase (dominant follicle \( \geq 16 \) mm) in 10/13 (77%) women (Brache et al., 1996). In two other studies in which levonorgestrel implants or depo-medroxyprogesterone acetate (DMPA) were inserted/administered within Days 8–13 of the menstrual cycle, ovulation occurred in 40 and 30% of implant and DMPA users, respectively, mostly within 72 h. Follicular outcome depended on E2 levels at the time of progestin administration, with follicular quiescence occurring more frequently in cycles in which E2 levels were low at administration, while ovulation occurred very frequently in cycles with high E2 levels at insertion, suggesting that if adequate E2 priming has occurred, the administration of an exogenous progestin provides the progestational signal required to induce ovulation (Petta et al., 1998a, b; Brache et al., 1999). Our data with the
administration of oral DSG are similar to the above studies regarding timing and occurrence of ovulation and are consistent with the 29% ovulation rate observed when a combined OC is initiated in the mid-follicular phase (dominant follicle ≥ 14 mm) (Baerwald et al., 2006).

Likewise, our results regarding the time required to achieve mucus impermeability after DSG administration are similar to those reported following late insertion of levonorgestrel implants or injection of DMPA (Days 8–13 of the cycle), when most of the subjects had a poor cervical mucus score and poor sperm penetration in vitro by Day 3 post initiation of treatment (Dunson et al., 1998; Petta et al., 1998a, b). Our study also confirms that UPA has no effect on cervical mucus as reported previously (Chabbert-Buffet et al., 2007; Jesam et al., 2015 submitted for publication).

This study, focused on quick-starting oral POP contraception, complements a recent study that evaluated the effect of UPA on quick-starting with a COC (Cameron et al., 2015). Cameron et al. observed a 33% ovulation rate when a COC is initiated after UPA in the mid-follicular phase, while the overall ovulation rate observed for the UPA + DSG cycles in the current study is 52%. This cannot be attributed to the size of the follicle or the E2 level at the time of treatment initiation, which were very similar in both studies. The ovulation rate observed in the Netherlands group was 33%, thus similar to the one observed in the study by Cameron et al., which had also recruited subjects at this center, together with two other European centers. It is thus possible that demographic differences between the DR and the European populations could explain the ovulation rate difference observed between the two studies. Finally, the effect of a progestin-only method on the risk of ovulation at mid-cycle could also be different from that of a COC, since the estrogenic component in COC enhances the suppressive effect of the progestin on the hypothalamic pituitary ovarian axis (Stanczyk et al., 2013).

Finally, it should be noted that these are only pharmacodynamic results, highlighting a potential interaction between a progestin agent and UPA; no actual efficacy in preventing pregnancy was measured.

This study provides information relevant to women who used EC in the context of failure of a barrier method or nonuse of any contraceptive method and who wish to initiate regular hormonal contraception immediately after using EC. The study did not address the situation where a woman uses UPA as EC after missing a few pills of an ongoing regular OC. Finally, this study has only tested the interaction between UPA and oral DSG 75 μg started the day after, near mid-cycle with high E2 levels, suggesting a possibly negative impact of a progestin agent on the capacity of UPA to postpone ovulation. Whether this applies to other regular progestin-only contraceptive methods administered by routes other than oral administration is unknown, though it may be possible.

In conclusion, the results from this study suggest that a continuous daily DSG 75 mg pill initiated the day after using UPA for EC may impair the ability of UPA to postpone ovulation for a sufficient period of time to preclude fertilization after unprotected intercourse. It also confirms that UPA has little impact on the contraceptive onset of a DSG POP and its ability to inhibit ovulation and cervical mucus. Together with the results from the study exploring a possible interaction with a COC, the results from the present trial suggest that it would be prudent to consider delaying the start of a regular oral contraception by a few days when advising women taking UPA for EC. A delay of 5 days, to preserve the potential of UPA to postpone ovulation beyond a timespan when sperm are believed to remain viable, seems reasonable.

Acknowledgements

The authors want to thank Ana Sofia Tejada, Elena de la Cruz, Aidelis Jorge and Margarita de los Santos, research staff at the Profamilia clinic, and the research staff at Dinox for their outstanding collaboration in the conduct of this study, making daily and weekend clinical visits throughout the duration of the study.

Statistical analyses were performed by Just Van Es at QPS, Petrus Campersingel 123 9713 AG Groningen, The Netherlands. Additional statistical input was provided by Bruno Scherrer, Saint-Arnould-en-Yvelines, France.

Authors’ roles

V.B. and D.P.L. were responsible for the initial concept and design of the study. All authors were involved in developing the design of the study and planning its implementation. V.B., L.C., C.K. and I.J.M.D. recruited and undertook assessments of subjects. D.P.L., N.K., and J.L.A. were responsible for the original draft of the manuscript, which was revised by all other authors. All authors gave their final approval of the final manuscript draft.

Funding

Funding was provided by HRA Pharma 75003, Paris, France.

Conflict of interest

V.B. has received funds for research studies, advice and lectures for HRA Pharma. C.K. and I.J.M.D. are directors of a contract research organization (Dinox) that received funds from HRA Pharma for the study conduct. D.P.L., N.K., C.M. and J.L.A. are HRA Pharma employees. L.C. has no conflict of interest in this work.

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