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ORIGINAL ARTICLE ***Fertility control***

A prospective, open-label, single arm, multicentre study to evaluate efficacy, safety and acceptability of pericoital oral contraception using levonorgestrel 1.5 mg

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STUDY QUESTION: Will the use of levonorgestrel (LNG) 1.5 mg taken at each day of coitus by women who have relatively infrequent sex be an efficacious, safe and acceptable contraceptive method?

SUMMARY ANSWER: Typical use of LNG 1.5 mg taken pericoitally, before or within 24 h of sexual intercourse, provides contraceptive efficacy of up to 11.0 pregnancies per 100 women-years (W-Y) in the primary evaluable population and 7.1 pregnancies per 100 W-Y in the evaluable population.

WHAT IS KNOWN ALREADY: LNG 1.5 mg is an effective emergency contraception following unprotected intercourse. Some users take it repeatedly, as their means of regular contraception.

STUDY DESIGN, SIZE, DURATION: This was a prospective, open-label, single-arm, multicentre Phase III trial study with women who have infrequent coitus (on up to 6 days a month). Each woman had a follow-up visit at 2.5, 4.5 and 6.5 months after admission or until pregnancy occurs if sooner, or she decided to interrupt participation. The study was conducted between 10 January 2012 and 15 November 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A total of 330 healthy fertile women aged 18–45 years at risk of pregnancy who reported sexual intercourse on up to 6 days a month, were recruited from four university centres located in Bangkok, Thailand; Campinas, Brazil; Singapore and Szeged, Hungary to use LNG 1.5 mg pericoitally (24 h before or after coitus) as their primary method of contraception. The participants were instructed to take one tablet every day she had sex, without taking more than one tablet in any 24-h period, and to maintain a paper diary for recording date and time for every coital act and ingestion of the study tablet, use of other contraceptive methods and vaginal bleeding patterns. Anaemia was assessed by haemoglobin evaluation. Pregnancy tests were performed monthly and pregnancies occurring during product use were assessed by ultrasound. At the 2.5-month and final visit at 6.5 months, acceptability questions were administered.

MAIN RESULTS AND THE ROLE OF CHANCE: There were 321 women included in the evaluable population (which includes all eligible women enrolled), with 141.9 woman-years (W-Y) of observation and with a rate (95% confidence interval [CI]) of 7.1 (3.8; 13.1) pregnancies per 100 W-Y of typical use (which reflects use of the study drug as main contraceptive method, but also includes possible use of other contraceptives from admission to end of study) and 7.5 (4.0; 13.9) pregnancies per 100 W-Y of sole use. In the primary evaluable

population (which includes only eligible enrolled women <35 years old), the rate was 10.3 (5.4; 19.9) pregnancies per 100 W-Y of typical use, and 11.0 (5.7; 13.1) pregnancies per 100 W-Y of sole use. There were three reported severe adverse events and 102 other mild adverse events (most common were headache, nausea, abdominal and pelvic pain), with high recovery rate. The vaginal bleeding patterns showed a slight decrease in volume of bleeding and the number of bleeding-free days increased over time. There was only one case of severe anaemia, found at the final visit (0.4%). The method was considered acceptable, as over 90% of participants would choose to use it in the future or would recommend it to others.

LIMITATIONS, REASONS FOR CAUTION: This was a single-arm study with small sample size, without a control group, designed as a proof of concept study to explore the feasibility of this type of contraception.

WIDER IMPLICATIONS OF THE FINDINGS: A larger clinical study evaluating pericoital contraception with LNG is feasible and our data show that this method would be acceptable to many women.

STUDY FUNDING/COMPETING INTEREST(S): This study received partial financial support from the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR) and the World Health Organization. Gynuity and the Bill and Melinda Gates Foundation (BMGF) provided financial support for project monitoring. HRA Pharma donated the LNG product. N.K. was the initial project manager when she was with WHO/HRP and was employed by HRA Pharma, which distributes LNG for emergency contraception. The other authors declare no conflicts of interest.

TRIAL REGISTRATION NUMBER: This study was registered on ANZCTR, Trial ID ACTRN12611001037998.

TRIAL REGISTRATION DATE: 4 October 2011.

DATE OF FIRST PATIENT'S ENROLMENT: 10 January 2012.

Key words: oral levonorgestrel / contraception / pericoital / effectiveness / anaemia

Introduction

Recent survey data and anecdotal information from sources in Africa, Latin America, Europe, and the USA suggested that many women are interested in an oral contraceptive pill (OCP) that is designed to be used only at the time of sexual intercourse (Arowojolu and Adekunle, 2000; Lerkiatbundit and Reanmongkol, 2000; Gilliam *et al.*, 2009; Taylor *et al.*, 2014). Such a method may have numerous advantages over daily OCP for women who have infrequent sex. For some women, taking an OCP only when needed may seem more intuitive than taking one every day even when sex has not occurred.

Users may find compliance easier with a coital-dependent pill regimen because pill-taking is triggered by a defined event and does not necessitate advance planning or routine intake. For most women, a coital-dependent pill regimen would require fewer doses than a daily pill regimen and would be more convenient. Furthermore, unlike other coital-dependent methods, such as condoms, diaphragms and spermicides, a contraceptive pill taken orally has the potential to be used without the cooperation or the knowledge of the male partner.

Levonorgestrel (LNG) when taken post-coitally has been studied extensively as a method of emergency contraception (EC) and the principal mechanism of action is to arrest or delay ovulation (Croxatto *et al.*, 2001, 2004; Marions *et al.*, 2002, 2004; Gemzell-Danielsson and Marions, 2004; Okewole *et al.*, 2007; Gemzell-Danielsson, 2010; Taylor *et al.*, 2014). When used very near to ovulation, LNG is much less effective than when used earlier in the follicular phase, contributing to lower efficacy estimates of post-coital use during this time frame. Precoital use of LNG is likely to be more effective at preventing pregnancy than post-coital use as it may simultaneously affect both cervical mucus and delay or arrest ovulation (Halpern *et al.*, 2014).

There is some information regarding repeated use of LNG as EC in the same menstrual cycle. A recent Cochrane review of repeated pericoital hormonal contraceptive use identified 12 clinical trials conducted in the 1970s and 1980s, including a total of 12 407 women who used the prescribed method for a total of about 1033 woman-years (W-Y) (Halpern *et al.*, 2014). These women represented a broad cross section of the female population in terms of age and reproductive history. In each of these trials, women were instructed to take 0.75 mg LNG immediately after (in most studies, within 1 h of) unprotected sex. In most trials, the observed coital frequency was a mean of about four times a month.

The Pearl Index (PI: number of pregnancies per 100 W-Y) in these studies ranged from 0 to 18.6 pregnancies per 100 W-Y and a combined figure was 5.1 pregnancies/100 W-Y (95% confidence interval [CI] 3.8, 6.7) (Halpern *et al.*, 2014). The efficacy of the method did not seem to be consistently related to any particular characteristic of the study population or to coital frequency. Overall, these data suggest that the efficacy of pericoital LNG was in the range of that of other coital-dependent contraceptives like the condom (Trussell, 2009, 2011).

The main side effects of pericoital use of 0.75 mg LNG were abnormal uterine bleeding, breast tenderness, dizziness, lower abdominal pain, fatigue, headache, weight gain, irritability, weakness and loss of libido. The incidence of these side effects was not clearly related to the frequency of tablet intake. Most subjects were satisfied with the method (Halpern *et al.*, 2014). However, the PI was high when LNG 0.75 mg was used, which is the main reason why 1.5 mg was chosen for the present study.

Despite the body of evidence about the use of LNG pill as EC, the potential of pericoital use of LNG 1.5 mg as a primary means of contraception has not yet been established. Consequently, the objectives of this proof of concept study were to evaluate the efficacy and safety of LNG 1.5 mg among women who expected to have sex on 1–6 days per month and who are relying on the study regimen as their primary method of contraception.

Materials and Methods

Study participants

This was a prospective, open-label, single-arm, multicentre Phase III trial study with women who have infrequent coitus (up to 6 days a month). The participants were enrolled at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, University of Campinas, Campinas, Brazil; the Department of Obstetrics and Gynaecology, Siriraj Hospital, Mahidol University, Bangkok, Thailand; the Department of Obstetrics and Gynaecology, National University Hospital, Singapore and the Department of Obstetrics and Gynaecology, Albert Szent-Gyorgyi Medical Centre, University of Szeged, Szeged, Hungary. The study was approved by the UNDP/UNFPA/UNICEF/World Health Organization (WHO)/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) Research Project Review Panel (RP2), the WHO Ethics Review Committee, and by the local ethics review board at each country site.

The study enrolled non-pregnant healthy fertile women of reproductive age (18–45 years) who had sex on between 1 and 6 days a month, were at low risk for sexually transmitted infections (STIs), were willing to use LNG 1.5 mg tablets as their primary contraceptive method, wanted to avoid pregnancy for at least the next 6.5 months after enrolment, were willing to accept an uncertain risk of pregnancy during the study, and understood that the risk of pregnancy on this method would be higher than other hormonal methods of contraception.

The exclusion criteria included being not at risk of pregnancy (currently pregnant, breastfeeding, recently post-partum, using an intrauterine device or had female or male sterilization); having a breast mass; or with contraindications to hormonal contraceptive use, and previous participation in the study or any other current medical research. The informed consent form, signed by all participants, included the nature, benefits and risk and instructions for use: 'Take one tablet every time you have sex, preferably before or as soon as possible after the sex act. You have up to 24 h before or after sex to take the tablet. Do not take more than one tablet in any 24-h period'. The women were counselled to take a second tablet if she vomited within 1 h after taking a study tablet. If she failed to follow the instructions (missed an indicated tablet), she was asked to contact the study site for advice about using EC pills. Tablets were provided in blister packages of 7 (provided by Delpharm Lille S.A.S; Lys-lez-Lannoy Cedex, France). Women were advised to use condoms if needed to protect against STI or human immunodeficiency virus. Furthermore, the women were instructed to maintain a paper diary, on which she recorded date and time for every coital act and ingestion of the study tablet, use of other contraceptive methods such as condoms, and occurrence of vaginal bleeding or spotting. Participants were instructed to bring the diary with them during follow-up visits.

Procedures

Each subject had an enrolment visit and three follow-up visits at 2.5, 4.5 and 6.5 months after admission. After assessment of eligibility, baseline data (including weight, blood pressure [BP] and haemoglobin [Hb]) level were collected, and each participant was provided with the study medication and instructions on use. At each follow-up visit, data about use of the study product and other contraceptives, vaginal bleeding, and adverse events (AE) were collected and a BP check and urine pregnancy test was performed. At the 2.5-month and final visit at 6.5 months, acceptability questions were administered. At the final visit, weight and Hb levels were rechecked. The site investigator team contacted each subject by telephone

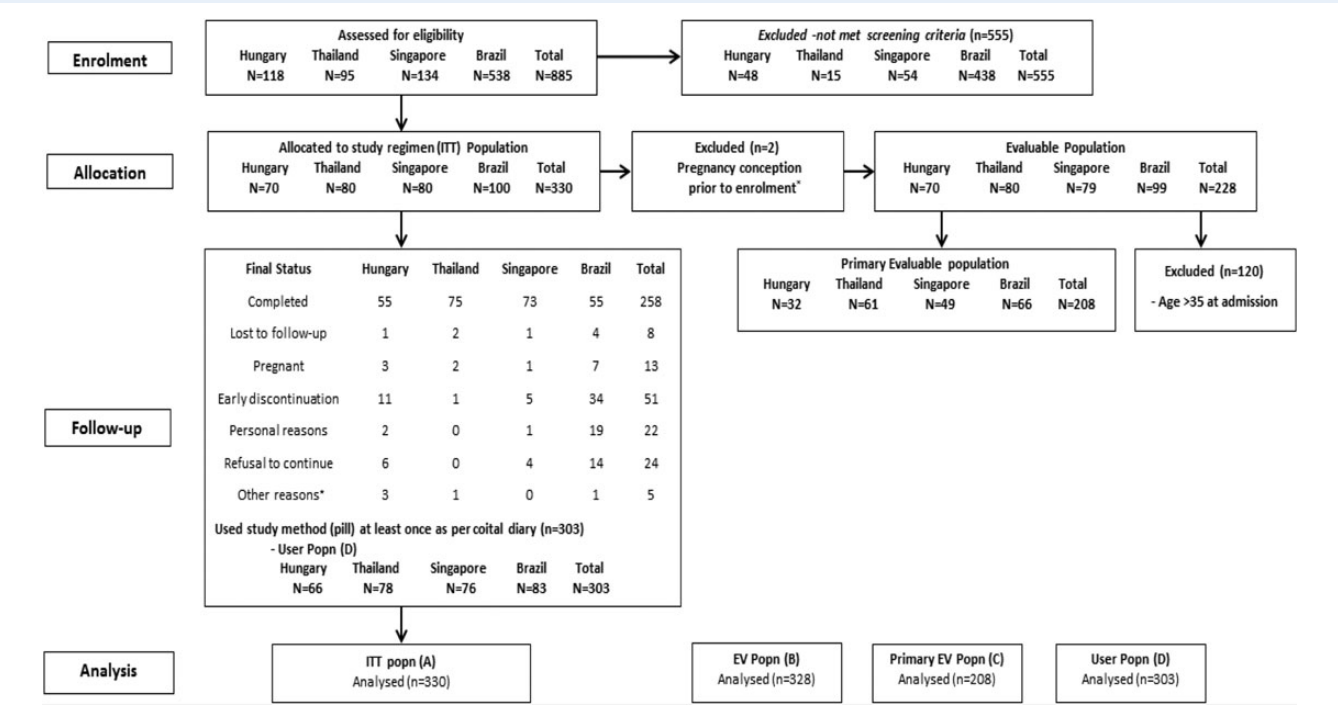

Figure 1 Participant flowchart for the study. *Two participants with pregnancy conception dated prior to enrolment (Singapore ID 3048, Brazil ID 4305). †Use of prohibited contraception ($n = 2$: Hungary, Brazil), stopped study pill ($n = 2$: Hungary, Thailand), health reasons ($n = 1$: Hungary). ITT Popn, intention to treat population; EV Popn, evaluable populations; Primary EV, primary evaluable population; User Popn, population.

between follow-up visits to ascertain the result of the home pregnancy test (performed each month where there was no in-clinic visit), to ask about continued use of the product, and to ensure that the subject had sufficient supply to last until the next scheduled visit. The site investigator team entered data into an electronic database and transmitted it electronically to the WHO for analysis. Pregnancies were ascertained by urine pregnancy tests at each visit, by home pregnancy tests between visits, and by subject self-report. Those with a positive urine pregnancy test had an ultrasound to confirm the pregnancy usually at 5–8 weeks gestation.

Data collection forms were reviewed for accuracy and completeness by study staff in-country. Data were double-entered into the OpenClinica web-based data management system version 3·1·3 (Akaza Research, Waltham, MA, USA). Validation checks and regular review of missing values, outliers, inconsistencies, and other errors were conducted.

Statistical analyses

All statistical analyses were performed using the SAS system for Windows. Release 9.3. 2011. (SAS Institute, Cary, NC, USA).

As a proof-of-concept study, the protocol established to enrol 300 women into the study. The primary efficacy analysis estimated the PI during sole use of the study medication among women at age of ≤35 years. This analysis would censor each subject's data on the date when she stopped considering the study product to be her primary contraceptive method and would exclude months in which a woman used any other method of contraception (such as condoms). Additionally, efficacy analyses estimated the PI during typical and perfect use of the product, and life-table analysis of pregnancy rates through 6 months of sole, typical and perfect use of the study product. Perfect use analysis excluded months during which the study product was not used according to instructions and typical use analysis included study months in which a subject used any other method of contraception in addition to the study pill.

Analogous analyses in the entire enrolled population and in specified subgroups were also conducted, with the following defined population groups: (i) Intent-to-treat population (ITT); referring to all subjects who were enrolled and provided study medication at the enrolment visit; (ii) Evaluable Population; referring to all subjects in the ITT population who provide any follow-up data except those who had admission criteria violations that may detract from an accurate analysis of efficacy; (iii) Primary Evaluable Population; referring to a subgroup of the Evaluable Population who were age of ≤35 years and (iv) User Population; including all subjects in the ITT population who used the study method at least once.

Safety analyses estimated the proportion of all subjects, including those over 35 years old, who had various safety outcomes of interest, including changes in vaginal bleeding parameters from baseline and other adverse events. Bleeding patterns were analysed according to the terminology proposed by the WHO (Belsey *et al.*, 1986; WHO, 1989) for users of progestin-only methods in 90-day reference periods as: *Amenorrhoea:* defined as no bleeding during the 90-days reference period; *Infrequent bleeding:* fewer than 3 bleeding episodes; *Frequent bleeding:* more than 5 bleeding episodes; *Irregular bleeding:* range of bleeding-free intervals exceeding 17 days; *Prolonged bleeding:* 1 or more bleeding episodes lasting 14 days or more; *light bleeding or spotting:* only light days; *medium bleeding:* at least 1 day of medium bleeding or no day of heavy bleeding; *heavy bleeding:* at least one or 2 days of heavy bleeding, with any number of light and medium days; *very heavy bleeding*: 3 or more days of heavy bleeding, with any number of light and medium days; *None of the above:* a 'normal' bleeding pattern.

Anaemia was categorized as mild (10–11 g/dl Hb), moderate (8–<10 g/dl Hb or a decrease from baseline of 2–4 g/dl) or severe (<8 g/dl Hb or a decrease from baseline of ≥4 g/dl) and reported using frequencies and percentages. Bleeding patterns and adherence were summarized according to the information captured in the diaries. The diary information was checked by

Table I Selected baseline characteristics of the participants in a study to evaluate the efficacy, safety and acceptability of pericoital oral contraception using levonorgestrel 1.5 mg.

Characteristics	*N* (%)
Race	
White	115 (34.8)
Black	23 (7.0)
Biracial	32 (9.7)
Asian	160 (48.5)
Highest educational level	
Never attended nor completed primary education	7 (2.1)
Primary	26 (7.9)
Secondary	131 (36.7)
Higher than secondary	166 (50.3)
Marital status	
Married or with life partner	258 (78.2)
Separated/divorced/widowed	8 (2.4)
Single	64 (19.4)
Number of live births (among those ever pregnant)	
None	21 (8.4)
1	124 (49.4)
2	71 (28.3)
3 or more	35 (13.9)
Ever used contraceptives	
Yes	307 (93.0)
Contraceptive methods used	
Oral contraceptive pills	243 (79.2)
Male condom	274 (89.3)
Injectables	99 (32.2)
Copper IUD or levonorgestrel intra-uterine system	90 (29.3)
Emergency contraceptive pills	87 (28.3)
Contraceptive ring or patch	17 (5.5)
Implants	15 (4.9)
Vaginal spermicide	8 (2.6)
Withdrawal	119 (38.8)
BMI, kg/m^2	
Underweight (<18.5)	19 (5.8)
Normal (18.5 to <25.0)	169 (51.2)
Overweight (25.0 to <30.0)	95 (28.8)
Obese (≥30.0)	47 (14.2)
Characteristics	
Age, years	
Mean (SD)	32.4 (6.8)
Range	18.0–45.4
Frequency of coitus, days in the past month	
Mean (SD)	4.1 (1.7)
Median (IR)	4.0 (3.0, 6.0)
Weight, kg	
Mean (SD)	64.1 (14.1)
Median (IR)	62.0 (55.0, 72.0)

Table II Contraceptive efficacy according to category of use.

Study population	n	Total number of pregnancies	Typical use* Total W-Y	Typical use* Incidence per 100 W-Y (95% CI)	Sole pill use** Total W-Y	Sole pill use** Incidence per 100 W-Y (95% CI)	Perfect pill use*** Total W-Y	Perfect pill use*** Incidence per 100 W-Y (95% CI)
Primary evaluable								
Overall	204‡	9†	87.10	10.3 (5.4, 19.9)	81.62	11.0 (5.7, 21.2)	81.14	11.1 (5.8, 21.3)
Hungary	32	2	13.02	15.4 (3.8, 61.4)	11.78	17.0 (4.2, 67.9)	11.78	17.0 (4.3, 67.9)
Thailand	61	2	29.24	6.8 (1.7, 27.4)	29.24	6.8 (1.7, 27.4)	29.24	6.8 (1.7, 27.4)
Singapore	49	0	23.23	–	20.86	–	20.82	–
Brazil	62	5	21.60	23.2 (9.6, 55.6)	19.74	25.3 (10.5, 60.9)	19.30	25.9 (10.8, 62.3)
Evaluable population								
Overall	321†	10†	141.92	7.1 (3.8, 13.1)	133.70	7.5 (4.0, 13.9)	133.05	7.5 (4.0, 14.0)
Hungary	70	3	30.24	9.9 (3.2, 30.8)	28.79	10.4 (3.4, 32.3)	28.79	10.4 (3.4, 32.3)
Thailand	80	2	38.40	5.2 (1.3, 20.8)	38.31	5.2 (1.3, 20.9)	38.31	5.2 (1.3, 20.9)
Singapore	79	0	37.56	–	34.49	–	34.45	–
Brazil	92	5	35.73	14.0 (5.8, 33.6)	32.11	15.6 (6.5, 37.4)	31.50	15.9 (6.6, 38.1)

‡A total of four participants excluded from primary evaluable population: aged ≤35 years but pill not primary contraception method.
†A total of nine participants excluded: Two (2) who became pregnant before enrolment (discovered during follow-up) and seven others who did not initiate pill use/pill not primary contraception method, it includes one woman who became pregnant at post-enrolment.
*Typical pill use considers total woman-years from admission to the date when participant stopped considering the study product to be her primary contraceptive method, and includes months in which a subject used any other method of contraception.
**Sole pill use considers total woman-years from admission to the date when participant stopped considering the study product to be her primary contraceptive method, and excludes months in which a subject used any other method of contraception.
***Perfect pill use considers total woman-years from admission to the date when participant stopped considering the study product to be her primary contraceptive method, and excludes months in which (i) pill use not sole, (ii) >1 pill within 24 h and (iii) vaginal sex but no pill intake.
W-Y, Women-years; CI, confidence interval.

staff in the presence of the woman against the relevant info in the follow-up form.

Acceptability analyses from all subjects included calculations of discontinuation rate by reason, as well as summaries of responses to the acceptability questions. Future contraceptive desires were assessed during 2.5 month and 6.5 month visits or at early discontinuation.

Results

The number of women assessed for eligibility, the number enrolled and the different analyses performed are shown in Fig. 1. Almost 50% of the subjects were Asian, and between 46 and 67% of the women were aged 25–35 years old. Baseline socio-demographic characteristics of the participants are shown in Table I.

Ten confirmed pregnancies occurred among the evaluable population during 141.9 W-Y of observation. The incidence per 100 W-Y (95% CI) was 7.1 (3.8; 13.1) for typical use and 7.5 (4.0; 13.9) during sole use in the evaluable population. In the primary evaluable population (less than 35 years old) wherein there were nine pregnancies, the rate was 10.3 (5.4; 19.9) pregnancies per 100 W-Y of typical use, and 11.0 (5.7; 13.1) pregnancies per 100 W-Y of sole use (Table II). In addition, almost 80% of the participants returned for the scheduled three visits and almost an equal proportion of women completed the study. The lost to follow-up was only 1.5% of the ITT population (Table III). The distribution of the pill intake by month of follow-up ranged from a mean of 4.2–6.9 in the first month to 4.3–6.2 by the sixth month of follow-up. The pill intake during the other months of observation was within the same range. Furthermore, no relationship was observed between the pregnancy rate and the frequency of pill intake per month of observation.

Regarding adverse events, most of those reported were mild and the most common were headache, nausea and abdominal and pelvic pain (Table IV). These occurred more often among women who took 4–6 pills per month. There were two participants who had severe adverse events, both assessed by the site investigators and authors to be not related to pill intake: one woman was admitted for choledocholithiasis for which she subsequently had surgery (last pill intake was 10 days before diagnosis) and the other had a ruptured corpus luteum cyst (last pill intake was 1 day before diagnosis).

Table III Self-reported adherence or compliance by the participants

Description	ITT (*N* = 330)	Evaluable (*N* = 328)	Primary evaluable (*N* = 208)	User (*N* = 303)
Number of women completing 6.5 months of follow-up	258/330 (78.2)	258/328 (78.7)	152/208 (73.1)	255/303 (84.2)
Number of women who used study pill as their primary method for 183 days or until pregnancy (if occurred ≤183 days)	323	321	204	303
Total number of woman-years using the study pill as the main contraceptive method	142.85	142.61	87.74	139.01
Total number of woman-years using only the study pill (study regimen)‡	134.95	134.71	82.59	131.11
Number of participants with completed follow-up scheduled study visits, *n* (%)				
1 visit	30/330 (9.1)	30/328 (9.1)	21/208 (10.1)	26/303 (8.6)
2 visits	10/330 (3.0)	10/328 (3.1)	10/208 (4.8)	10/303 (3.3)
3 visits	258/330 (78.2)	258/328 (78.7)	152/208 (73.1)	255/303 (84.1)
Number of participants who:				
– Completed study, *n* (%)(Participant used study pill as the primary method for up to at least 183 days or became pregnant during product use before 183 days.)	270/323* (83.6)	268/321 (83.5)	161/204 (78.9)	266/303 (87.8)
– Discontinued early, *n* (%)(Participant discontinued use of study product as their primary method before 183 days while not known to ever have become pregnant during its use.)	48/323* (14.9)	48/321 (15.0)	38/204 (18.6)	36/303 (11.9)
– Lost to follow-up, *n* (%)(Participant neither completed 183 days follow-up nor discontinued early (if <183 days) and the time she stopped using the study pill as primary method nor whether she became pregnant during its use is unknown.)	5*/323* (1.5)	5*/321 (1.5)	5*/204 (2.5)	1/303 (0.3)

*Seven (7) participants IDs 4185, 4264, 4328, 4376, 4449, 4463 & 4487 (all from Brazil site) were excluded from method discontinuation/pill use analysis, since available data show no indication that their primary method of contraception was study pill nor that study pill was ever used during sex act. Of these, three (3) were lost to follow-up (: IDs 4185, 4449, 4463).
‡Six (6) participants commenced using study pills together with other types of contraception not included: Ids 1018 & 1098 (Hungary), 3071 & 3101 (Singapore), 4195 & 4502 (Brazil)—excluded from person year estimation.
ITT, intent-to-treat population.

Vaginal bleeding patterns are presented in Fig. 2. The categories may not be mutually exclusive, as frequency, regularity, days of bleeding and volume are all considered in the description. In general, the women experienced prolonged bleeding only during the intake of the first 10 pills. Frequent bleeding did not change during the period of observation and with the number of used pills. Furthermore, lighter bleeding periods were observed and very heavy bleeding decreased with higher pill intake through the months of the study. Rates of anaemia were low in this population group. Moderate anaemia (from 8 to 10 g/dl) decreased from 5 out of 330 women (1.5%) at baseline, to 2 out of 258 women (0.8%) at final study visit. There was only one case of severe anaemia, found at the final visit (0.4%) after taking a total of 24 pills over the full observation period.

Acceptability was assessed at the 2.5 and 6.5 months visits. Most of the women would use this method in the future if it was available and would recommend it to other women. Furthermore, we asked about reproductive intention to see if their responses correlated with how well they used the study pills. A total of 12.1% of the women reported some sexual intercourse without taking the pill (Table V).

There are additional analyses presented in the Supplementary Tables. Supplementary Table S1 would show that there is no clear pattern of pill intake per month of follow-up among the user population that included women who took the tablet at least once. Supplementary Table S2 would show the number of pregnancies by the frequency of pill intake per menstrual cycle in the primary evaluable population. Supplementary Table S3 shows the percentage distribution of most common side effects by the number of times LNG was taken per month.

Discussion

Pericoital use of 1.5 LNG as a regular contraceptive method is effective, with few mild side effects and with high acceptability. The observed pregnancy rate is comparable to that reported for other coitally-dependant contraceptive methods (Trussell, 2009, 2011).

Previous studies of pericoital use using 0.75 mg of LNG (which is half the dose used in the present study) found similar or higher pregnancy rates (Halpern *et al.*, 2014; Taylor *et al.*, 2014), which may be due to the difference in LNG dose, the characteristics of women included, the study sample size, or the difference in the number of sex acts per month during the period of observation. Different contraceptives have different characteristics that would fit into the needs of the woman. The use of LNG 1.5 mg as pericoital contraceptive would be less efficacious than other modern methods taken continuously or are long acting methods. Ideally LNG 1.5 mg can be used by women who are not already using contraception or are only using barrier methods.

Table IV Summary of adverse events (AE).

Characteristics	N (%)
Study site	
Brazil	48 (47.1)
Hungary	27 (26.5)
Singapore	3 (2.9)
Thailand	24 (23.5)
Degree of severity	
Mild	79 (77.5)
Moderate	20 (19.6)
Severe	3 (2.9)
Relatedness	
Probably related	42 (41.2)
Probably not related	60 (58.8)
Required participant to stop using the pill because of the AE	
No	96 (94.1)
Yes	6 (5.9)
Outcome of the AE	
Recovered without sequelae	89 (87.2)
Recovered without sequelae	2 (2.0)
Ongoing as of last visit	11 (10.8)
Most common AE (more than 3 reports)	
Headache	15 (29.3)
Nausea	6 (16.3)
Abdominal and pelvic pain	6 (16.3)
Influenza	4 (10.9)
Acne vulgaris	3 (8.1)
Candidiasis	3 (8.1)

Although different studies with the use of LNG 0.75 mg after unprotected sexual intercourse showed a PI from zero to 18.6 per 100 W-Y (Halpern *et al.*, 2014), the three larger multicentre studies with 915 participating women presented a PI from 6.8 to 18.0 pregnancies per 100 W-Y, with a pooled PI of 8.9 per 100 W-Y (95% CI 5.1–14.4) (Bhattacharjee *et al.*, 1987; He *et al.*, 1991; WHO, 2000; Halpern *et al.*, 2014), which is slightly lower than the PI for the primary efficacy analysis (11.0) and only slightly higher than the PI for the entire evaluable population in the present study.

The prior studies of postcoital LNG regimens had limitations. First, many of the study reports are dated, brief and vague and many details relating to the study procedures and findings are not included. Because most of the studies were conducted before year 2000 (Halpern *et al.*, 2014), this problem does not appear to be remediable. Second, the prior studies did not collect some data of interest, such as measures of anaemia, which is an important safety consideration in use of a method that could cause abnormal vaginal bleeding. Finally, the trials were conducted with LNG 0.75 mg and the steroid was taken exclusively after sexual intercourse. Data showing that ECs are more effective if taken close to the time of sexual intercourse suggest that a regimen that can be used either before or after intercourse may have the potential to optimize contraceptive efficacy (Piaggio *et al.*, 2011). EC with LNG is recommended using a single dose of 1.5 mg; it has similar efficacy to two doses of 0.75 mg taken 12 h apart, and the single-dose regimen simplifies the drug use without an increase in side effects (von Hertzen *et al.*, 2002; Dada *et al.*, 2010).

A contraceptive pill which can be taken only when the woman has sexual intercourse may have a number of advantages for women who have sex infrequently. Many women have infrequent sex for many reasons, including a partner who is not always at home, such as sailors, military personnel and those in prison. Furthermore, it may reduce the amount of steroid intake and it is private, which is important mainly among adolescents. Additionally, this method could reduce the possibility of forgetting to take a pill, as it is taken close to sexual intercourse itself.

Despite the fact that postcoital contraception with oral LNG as EC has been extensively evaluated in numerous studies and it is registered in many countries, information about the pericoital EC use of 1.5 mg LNG is scarce. The evidence for its repeated use, either as a regular contraceptive or as EC, is limited, and especially on the perceived higher rates of side effects and lower contraceptive effectiveness when compared with other modern contraceptives (Bhattacharjee *et al.*, 1987; ACOG, 2012; WHO, 2012).

Regarding bleeding patterns, our results showed that the only one which could be inconvenient was frequent bleeding, which was observed through the entire period of the study and independent of the number of pills the women takes. A previous study (Bhattacharjee *et al.*, 1987) assessed the side effects of postcoital LNG 0.75 mg used repeatedly (mean $\pm$ SD 4.0 $\pm$ 2.6 tablets) during one cycle. The overall effect of LNG upon bleeding patterns—mainly cycle length—was insignificant; however, intermenstrual bleeding or spotting was observed in 8.5% of the treated cycles and 12.5% of the irregular cycles. Others did not observe an association between cycle control and the number of pills taken (Bhattacharjee *et al.*, 1987; He *et al.*, 1991).

The three reported serious adverse effects in this study were, in the judgment of the investigators, not related to the study product. One participant had cholelithiasis, and had a cholecystectomy, which were reported as two adverse events. The other was a case of haemorrhagic corpus luteum cyst, which was removed within the same day. The incidence of side effects was low and these were in general mild and many not related to the study pill, as described previously (Taylor *et al.*, 2014) and also not related to the number of pills taken (Supplementary Table S3). Furthermore, the observed high acceptability is consistent with previous reports which showed acceptability ranging from 49 to 81% (WHO, 2000; Taylor *et al.*, 2014) and may indicate that side effects were not very important to the participants.

There were methodological limitations in this study. This study was designed as a basis for future trials, targeting a group of women who have infrequent sex, in as many sites and countries as possible. In some sites, recruitment and follow-up were efficient; however, in the site in Hungary, recruitment of study participants took more than 18 months.

In conclusion, this study showed that the regular use of LNG 1.5 mg pericoitally in women who have infrequent sex is a safe strategy and, in general, is a well-tolerated method of contraception for women. The contraceptive efficacy was higher than women who do not use contraception and comparable to women who used coitally-dependent contraceptives. The proportion of women who will be eligible to use this kind of contraception is not easy to estimate. However, reports have shown unintended pregnancies are almost 50% in different settings. Many of these

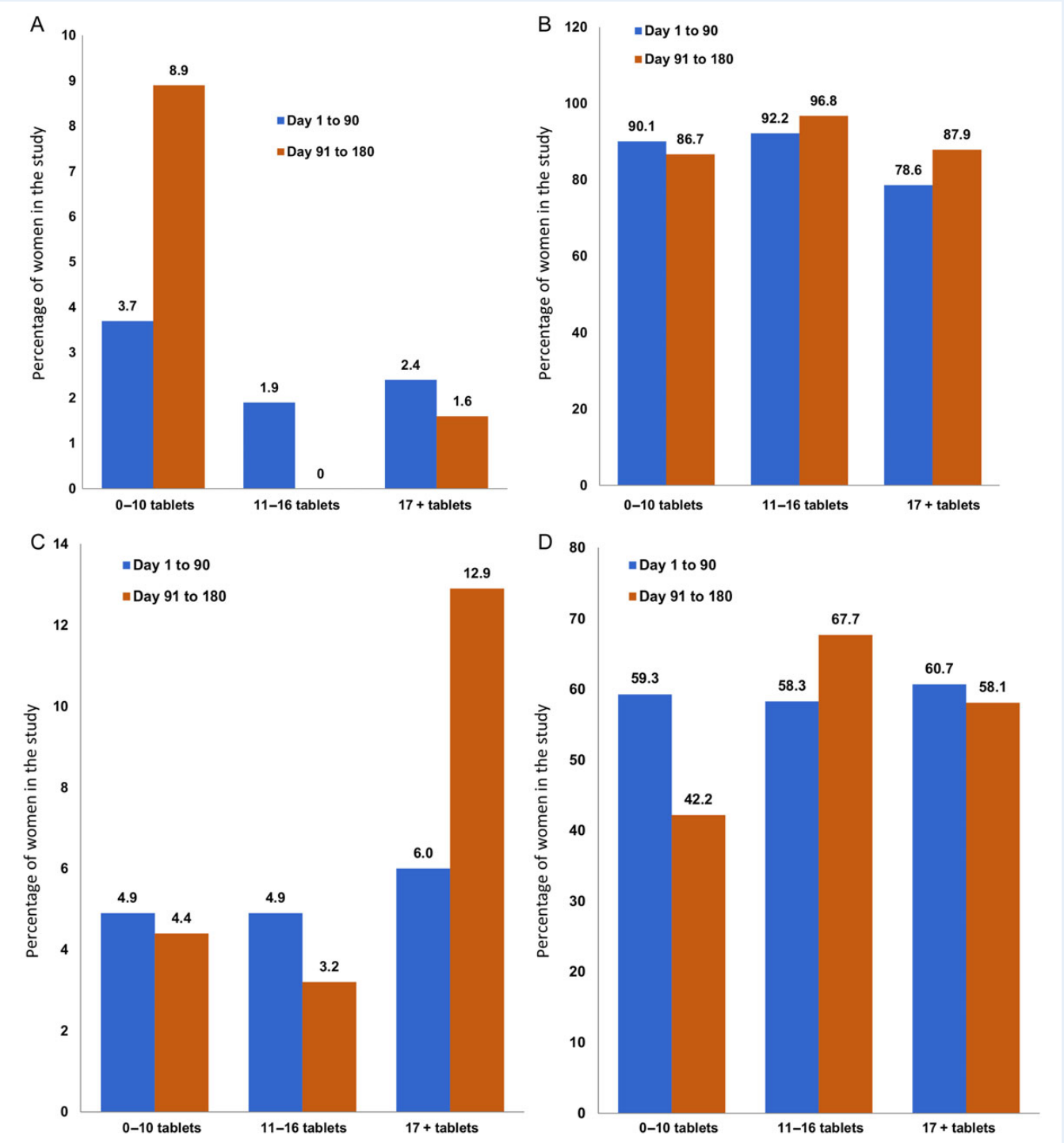

Figure 2 Frequency of irregular bleeding patterns per 90 day study period based on number of tablets taken: (**A**) prolonged vaginal bleeding (at least one bleeding episode lasting 14 days or more during the reference period of 90 days); (**B**) frequent vaginal bleeding episodes (defined as having more than five bleeding episodes throughout the reference period of 90 days); (**C**) light vaginal bleeding episodes; (**D**) medium vaginal bleeding episodes (at least 1 day of medium with any number of light bleeding days recorded during the episode, and no days of heavy bleeding); (**E**) heavy vaginal bleeding episodes (at least 1 or 2 days of heavy bleeding recorded, with any number of light and medium days, during the episode) and (**F**) very heavy vaginal bleeding episodes (three or more days of heavy bleeding recorded during the episode, with any number of light and medium days).

women may not be using regular contraceptives because they have infrequent sex, as reported in the USA (Herbenick *et al.*, 2010). Pericoital use (on demand, i.e. taken only when having sexual intercourse, or less frequent but repeated use) of LNG 1.5 mg could help in the reduction of unintended pregnancies and this research provides valuable information about the repeated use.

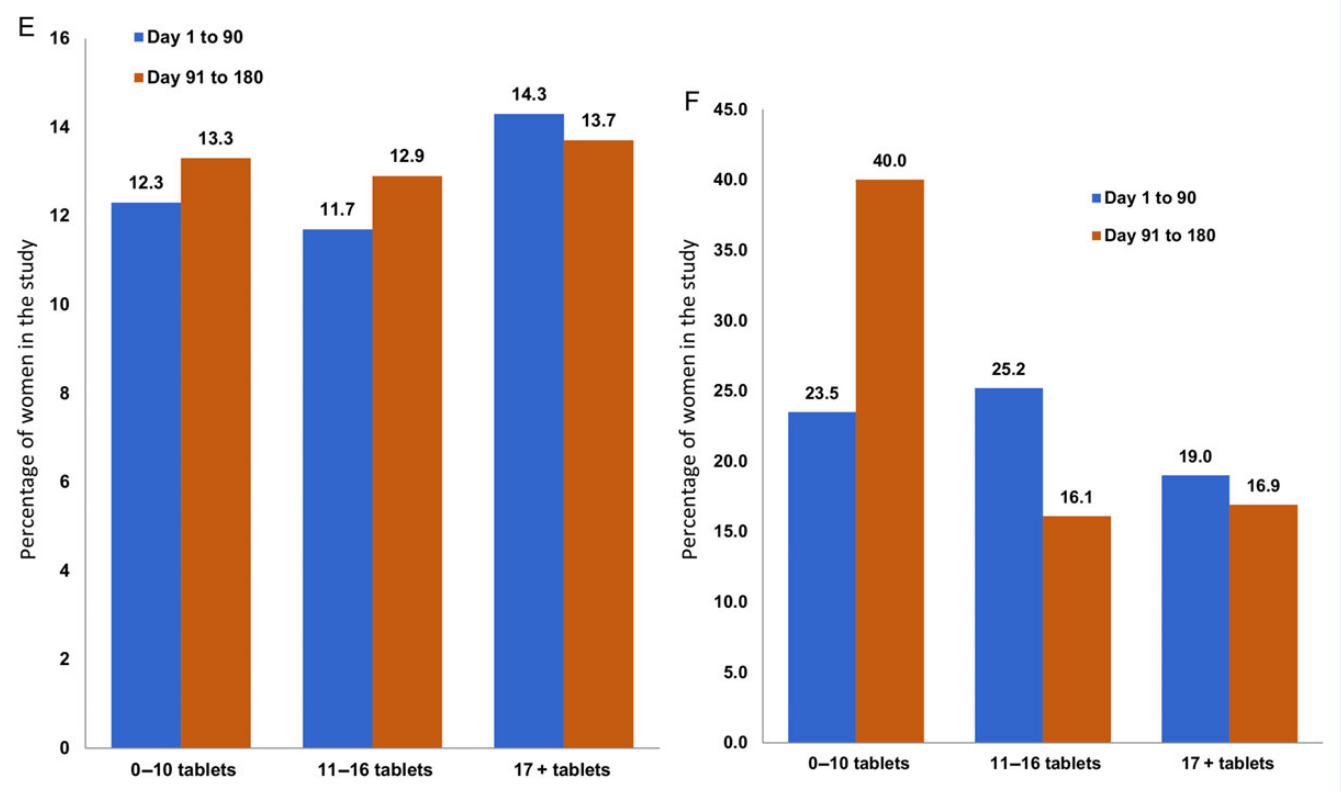

Figure 2 Continued.

Table V Acceptability indicators.

Questions	At 2.5 months *N* (%)	At 6.5 months *N* (%)
If the study pills were shown to be effective for preventing pregnancy, and they were available outside the study, do you think you might want to use them for contraception in the future?		
No	11 (3.7)	3 (1.2)
Yes	275 (92.3)	247 (95.7)
Don't know	12 (4.0)	8 (3.1)
If the study pills were shown to be effective would you recommend the study pills as a method of contraception for other women?		
No	5 (1.7)	1 (0.4)
Yes	286 (96.0)	252 (97.7)
Don't know	7 (2.3)	5 (1.9)
Were there ever times when you had sex and did not use the study pills?		
No	261 (87.6)	243 (94.2)
Yes	36 (12.1)	15 (5.8)
Don't know	1 (0.3)	0 (0.0)
Do you want any (more) children ever in the future?		
No	130 (43.6)	119 (46.1)
Yes	143 (48.0)	115 (44.6)
Don't know	25 (8.4)	24 (9.3)

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors' roles

N.K., L.B., G.B., K.S., M.T., M.P.R.F., N.H., and T.M.H.N. conceived the study and were responsible for developing the protocol, analysing and interpreting the data. Aside from the already mentioned investigators, A.G., T.B. and M.V.B. participated in the enrolling the subjects and management of the project at their respective centres. M.P.R.F. and L.B. were responsible for coordinating the writing and revising the final version of the manuscript.

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Conflict of interest

N.K. was previously employed by HRA Pharma.

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