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Original Article

A Randomized, Controlled Trial of Levonorgestrel Vs. The Yuzpe Regimen as Emergency Contraception Method among Iranian Women

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Abstract

Background: We aimed to compare acceptability of Levonorgestrel with the Yuzpe regimen among Iranian women based on their side-effects and resulting changes in the amount and pattern of menses.

Methods: Five hundred twenty nine participants aged 15-49 having regular menses and one act of unprotected intercourse within 72 h were included in the double-blind, controlled trial in 2006-2007 and randomly assigned into LNG (n=263) and HD (n=266) groups, receiving Levonorgestrel 0.75 mg given 12 h apart and ethinyl estradiol 100 µg plus 0.5 mg Levonorgestrel 0.5 mg repeated after 12 h, respectively.

Results: The participants receiving Levonorgestrel experienced significantly lower side-effects in the case of nausea, vomiting, and dizziness ($P<0.05$). The changes occurred in the amount and pattern of menses were the same for both groups ($P>0.05$). No significant difference was observed between the efficiencies of the treatments.

Conclusion: Significantly lower side-effects of Levonorgestrel can be considered as greater acceptability and translated to higher efficiency.

Keywords: Levonorgestrel, Yuzpe regimen, Emergency contraception, Side-effects

Introduction

Seventy five million unwanted pregnancies annually occur in the world, 50 million of which lead to termination of pregnancy and 20 million ends up with unsafe abortions. It results to 55000 deaths happen in the world, particularly in developing countries (95%) (1). The number of unwanted pregnancies in Iran, as a developing country, is about 500000 annually, 16% of which leads to termination of pregnancy (2). The main reasons for unwanted pregnancies are failure of contraceptive methods such as condom breakage or slippage and miscalculation of infertile period, or in some situations forced sex and unmet need (3). This can, however, be easily prevented by using emergency contraceptive pills (ECPs) or so-called "morning-after pills" that are considered to be effective if taken within 5 days of unguarded intercourse (4), though it was priory believed that they have to be taken within 72 h. This method can highly decrease the costs posed to health care providers due to unwanted pregnancies (5-7).

The first emergency contraceptive method was introduced by Yuzpe(8) which is called "Yuzpe regimen". Afterwards, the efficacy of the method was evaluated by several studies and it was found that the Yuzpe regimen is quite an effective method of emergency contraception (9), but it has some side effects such as vomiting, nausea, dizzi-

ness, and fatigue (10). Mifepristone and Danazol have also been introduced as alternative methods of emergency contraception and assessed by various studies. Danazol was found to be an inefficient method of contraception (11). Mifepristone, however, is an effective method of contraception (12), have milder side effects than Yuzpe(13), but because it affects menstrual cycle (11) and is associated with induced abortion (10), it is not widely used. Because of disadvantages of all aforementioned contraceptive methods, a new regimen, called "Levonorgestrel only", was proposed (14) and its efficacy and side effects have been highly evaluated. The most comprehensive, multicenter, randomized controlled trial on the efficacy of Levonorgestrel only showed that efficacy of this method is higher than that of Yuzpe regimen by a factor of 3 and has considerably fewer side effects (15). The findings were supported by another RCT (16). There are two regimens of Levonorgestrel: A double o.75 mg dose of Levonorgestrel taken 12 h apart; and a single 1.5 mg dose. Both mentioned regimens have the same effectiveness (4, 17, 18), so with the advent of the single-dose method, use of hormonal contraceptives can be highly simplified, particularly if taken in the afternoon (19). Other aspects of ECP_s are well described and discussed in the literature (20-22).

The only problem that remains unsolved is the change occurs in normal time and length of menstrual bleeding due to use of ECP_s (3), particularly in the case of Levonorgestrel (23, 24). On the other hand, the time and length of spotting is quite important for Iranian women because every change in the time and length of menses affects their religious activities and interferes with them. In addition, few studies have been conducted in Iran exploring the efficacy of Yuzpe regimen compared to Levonorgestrel (25, 26). However, these studies were conducted using very small sample sizes and did not measure the serum levels of Beta-HCG before administrating the pills.

The present study, therefore, aimed at evaluating the pattern of menstrual bleeding in the two efficient methods of emergency contraception, namely, Levonorgestrel only and Yuzpe regimens among woman in Gilan province, Iran, who had had unguarded intercourse and seeked post coital contraception. We also assessed the efficacy, side effects, and acceptability of aforementioned method in participants. Results of this study can be used for future policy making on the best and the most acceptable method of emergency contraception according to cultural and religious beliefs in Iran.

Materials and Methods

Protocol

Eligible participants were sexually active women aged between 15 and 49 years having regular menstrual cycles of 24-42 days. We also included women having only one act of unprotected intercourse within current cycle and they were asked to take the pills within 72 h of the unprotected intercourse. In addition, the failed contraceptive method was determined to be condom or conventional method. Breast-feeding women were also included provided that their baby was older than 6 months. Exclusion criteria were breast-feeding women with their baby younger than 6 months, hormonal contraindications in their current cycle, use of hormonal contraceptives, uncertainty about the time of LMP, and suspected pregnancy.

Between 12 Sep 2006 and 25 Jun 2007 after complying with inclusion criteriaparticipants were asked to sign the written consent. Participants were then classified into two groups (i.e. HD regimen and LNG regimen groups) according to balanced black randomization. Four tablets in the same size, shape, and color were put in each set. Neither the obstetrics, nor the participants were aware of the type of tablets in each set (double-blind). Only the person responsible for randomization was aware of the contents of the sets according to the serial numbers stuck on the sets. Levonorgestrel regimen (LNG group) consisted of two sets; each one contained a 0.75 mg Levonorgestrel and a placebo tablet; the pills in each set were taken at once and the sets were taken 12 h apart. Yuzpe regimen (HD group) consisted of four white tablets; two HD pills were put in a set. The pills in each set were taken at once and the sets were taken 12 h apart. The third dose (two pills) was also given to the participants to be taken if regurgitating within two hours of drug ad-

ministration. The first set of tablets was taken in presence of the obstetrics and the second set was taken at home 12 h later. The article was registered formally as the following code: IRCT ID: IRCT2013091112307N2.

Data collection and follow-up

The first form that was filled out by the midwife at the first day consisted of questions on demographic characteristics and medical status of the participantants. Their weight and height were also measured to calculate BMI. On the second form, participants were asked to write down the time of administration of the second dose and any possible side effects experienced. Third form was filled out by the midwife one week after expected menses and contained information regarding possible changes occurred in normal pattern of menstrual bleeding. Side effects were only assessed among participants who had met drug administration criteria.

Sample size calculations

According to the most comprehensive study on the efficacies of Levonorgestrel and Yuzpe regimens (15), only 2.1% difference exists between pregnancy rates of above mentioned methods. Hence, power calculations revealed that 744 participants in each treatment group would have needed if the same difference had expected to be observed in our society.

Data analysis

Having handled the outlier data, descriptive analyses was conducted using SPSS software. Group-specified descriptive analyzes were then performed for both treatment groups. Afterwards, comparisons were made between the two groups employing chi-square and *t*-test. Outcome measures were then compared between treatment groups. Having done the analyses, data were decoded and the results were assigned to each group.

Results

Five hundred twenty nine women met eligibility criteria and participated in this study (two hundred sixty six women in HD group and two hundred sixty three women in LNG group), among which four hundred forty eight women lived in Rasht and eighty one women lived in Bandar Anzali, northern of Iran. No statistically significant differences were observed in job, level of education, living area, and previously used contraceptive method between treatment groups.

Table 1 shows baseline characteristics of eligible participants. Because of effective randomization, no statistically significant differences were observed in baseline characteristics of the two groups. Majority of the participants were in their late 20s (average 28.8 years old) and almost half of each group had previously used condom as the method of contraception. The participants in both groups were also equal in the knowledge of emergency contraception (Table 2) and one third in each group had experienced use of emergency contraceptive pills.

Table 1: Baseline characteristics of eligible participants

Variable		Mean (SD) in HD group	Mean (SD) in LNG group	Mean (SD) total	*P* value (chi-square)
Age		28.8 (6.2)	28.8 (5.6)	28.8 (5.9)	0.874
Weight		66.7 (12.1)	67.4 (11.4)	67.0 (11.7)	0.493
Height		159.4 (5.8)	160.0 (5.5)	159.6 (5.7)	0.257
BMI		26.3 (4.6)	26.3 (4.2)	26.3 (4.4)	0.893
Number of pregnancies		1.8 (1.1)	1.7 (1.1)	1.8 (1.1)	0.484
Number of childbirth		1.5 (0.7)	1.4 (0.8)	1.5 (0.8)	0.862
Number of abortions		0.3 (0.7)	0.3 (0.6)	0.3 (0.6)	0.252
Frequency (percentage) of prior contraceptive method	Condom	142 (54%)	167 (48.8%)	269 (51.4%)	0.239
	Conventional	121 (46%)	133 (51.2%)	254 (48.6%)	

Table 2: Knowledge and prior experience of emergency contraception among participants in both treatment groups

Variable	Status	Frequency (Percentage) in HD group	Frequency (Percentage) in LNG group	Frequency (Percentage) total	*P* value (chi-square)
Knowledge of ECPs	Perfect knowledge	21 (8)	22 (8.6)	43 (8.3)	-
	Know HD and LD pills	122 (46.4)	118 (46.3)	240 (46.3)	
	Do not know number of pills	4 (1.5)	5 (2)	9 (1.7)	
	Know the access method	48 (18.3)	60 (23.5)	108 (20.8)	
	Do not know ECPs	68 (25.9)	50 (20)	118 (22.8)	
Prior use of	Yes	89 (33.6)	176 (32.4)	174 (66.7)	0.78
ECPs	No	85 (66.4)	177 (67.6)	353 (32.9)	
Status of prior ECPs use	Correct	77 (83.7)	68 (78.2)	145 (81)	0.573
	Incorrect	11 (12)	15 (17.2)	26 (4.5)	
	Do not remember	4 (4.3)	4 (4.6)	8 (14.5)	

Time intervals between unprotected intercourse and the first and the second administration of ECPs in both treatment groups are given in Table 3. Majority of the participants (66.5% in HD group and 66% in LNG group) had used the tablets within 12 h of unguarded intercourse. No case of drug administration after 72 h was reported. Seven women in HD group versus one woman in LNG group had not taken the second dose (P = 0.059). Percentage of correct use of ECPs (including the act of intercourse within one week of drug administration) was significantly higher in HD group.

Table 3: Status of drug administration among participants

Variable	Status	Frequency (Percentage) in HD group	Frequency (Percentage) in LNG group	Frequency (Percentage) total	*P* value (chi-square)
Time interval between coitus and drug administration	< 12 h	177 (66.5)	173 (66)	350 (66.3)	0.961
	12-24 h	31 (11.7)	30 (11.5)	61 (11.6)	
	24-48 h	45 (16.9)	48 (18.3)	93 (17.6)	
	48-72 h	13 (4.9)	11 (4.2)	24 (4.5)	
Time interval between doses	< 12 h	241 (90.6)	237 (90.1)	487 (90.4)	0.059
	12-24 h	18 (6.8)	25 (9.5)	43 (8.1)	
	Did not take	7 (2.6)	1 (0.4)	8 (1.5)	
Status of ECP use	Correct	186 (69.9)	161 (61.2)	347 (65.6)	0.035
	Incorrect	80 (30.1)	102 (38.8)	182 (34.4)	
week of drug administration	Yes	86 (32.6)	123 (46.9)	209 (39.7)	0.001
	No	178 (67.4)	139 (53.1)	317 (60.3)	

The rate of unwanted pregnancies due to unprotected intercourse was higher among participants in LNG group compared to HD group. Four women (1.5%) in LNG group had become pregnant, compared to three women (1.1%) in HD group, though the difference was not statistically significant ($P = 0.723$).

Frequency and severity (only in the case of nausea) of side effects of both Levonorgestrel and Yuzpe regimens are given in Table 4. 75% of the participants in LNG group had not experienced nausea at all, and 19.8% had had mild nausea. In contrast, 62% of the participants in HD group had experienced mild and severe nausea, which is significantly higher than that of LNG group. In addition, frequency of vomiting and dizziness were also significantly higher in HD group. Fatigue and headache were more observed in HD group, though the difference was not significant. In the case of other side effects, no differences were observed.

Finally, the amount of menstrual bleeding before and after drug administration is given in Table 5. The level of the change occurred in bleeding patterns of each group is also shown in this table. The menstrual bleeding after drug administration had occurred more heavily, compared to that before the drug administration. However, since the change had occurred in both groups, no statistically significant change observed in menstrual bleeding pattern due to drug administration between treatment groups.

Table 4: Frequency of side effects within one week of drug administration

Side effects		Frequency (Percentage) in HD group	Frequency (Percentage) in LNG group	Frequency (Percentage) total	*P* value (chi-square)
Vomiting	Severe	66 (24.8)	12 (4.6)	78 (14.7)	< 0.001
	Moderate	99 (37.2)	52 (19.8)	151 (28.5)	
	Mild	101 (38)	199 (75.7)	300 (56.7)	
Nausea		73 (24.7)	9 (3.4)	82 (15.5)	< 0.001
Headache		122 (45.9)	106 (40.3)	228 (43.1)	0.197
Fatigue		124 (46.6)	102 (38.8)	226 (42.7)	0.069
Dizziness		125 (47)	98 (37.3)	223 (42.2)	0.023
Breast tenderness		51 (19.2)	58 (22.1)	109 (20.6)	0.413
Stomach pain		106 (39.8)	105 (39.9)	211 (39.9)	0.986
Nose spot		56 (21.1)	61 (23.2)	117 (22.1)	0.553
Diarrhea		54 (20.3)	50 (19)	104 (19.7)	0.709

Table 5: Amount of menstrual bleeding before and after drug administration and the resulting changes in menstrual bleeding patterns

Variable	Mean (SD) in HD group	Mean (SD) in LNG group	Mean (SD) total	*P* value (chi-square)
Spotting before drug administration	38.8 (21.9)	40.3 (21.8)	39.5 (21.8)	0.428
Spotting after drug administration	35.2 (22.8)	38.7 (25.5)	36.9 (24.2)	0.093
Change of spotting pattern	-3.6 (22.1)	-1.5 (25.5)	-2.6 (23.8)	0.326

Discussion

According to the results from present study, complete knowledge of emergency contraception is quite low among women in Gilan province, Iran (only 8% in HD group and 8.6% in LNG group had sound complete knowledge about ECPs), which is consistent with results from other studies. Although quite critical, knowledge of ECPs is very low in developing countries such as Cameron (27),

Uganda (28), Nigeria (29), and South Africa (30), even among health care providers (31), compared to that in highly developed countries such as USA (32). This is the most important reason for the low rate of ECP use in such countries and brings about the need for extensive education of ECPs for sexually active women. Extensive education combined with increased access to ECPs through pharmacies without prescription as an over-the-counter medicine can highly increase the rate of ECP use and reduce the medical costs posed to society due to unwanted pregnancies (5-7), as experienced in USA and England (33, 34).

We failed to distinguish a statistically significant difference in pregnancy rates between the treatment groups that was previously observed by other randomized controlled trials (15, 16). The first reason can be assigned to the low number of sample size. According to Task Force on Postovulatory Methods of Fertility Regulation (15), if a 2.1% difference had to be distinguished in our society, 744 participants would have needed in each group. In our study, however, 529 compiled with eligibility criteria were classified into two groups (266 women in HD group and 263 women in LNG group). This implies inadequate power of the present study to distinguish a significant difference in efficiencies of the treatment groups. The other reason can be assigned to greater number of intercourse within one week of drug administration in LNG group due to having lower side effects, which lowers the efficiency of the Levonorgestrel group.

Nonetheless, our study has some advantages over the previous studies conducted in Iran. The study of Farajkhoda et al. (25) was conducted with a small sample size. This combined with the low rate of expected pregnancy led to a negligible statistical power in revealing the possible difference between the efficiency of the two methods (with only 62 and 60 individuals in intervention and control groups, respectively). In addition, they did not measure the serum level of Beta-HCG at the time of administering the pills. Therefore, they could not have left out the possibility of pregnancy from previous cycles. In other words, there was still the possibility that some of the participants had gotten pregnant from previous unprotected intercourses. In this situation, there is no indication for administration of the drug at this stage. This effect can undermine the validity of the findings with respect to the efficiency of the drug. In another study conducted by Broomandfar et al. (26) in Iran, although the authors pointed out a significant difference between the efficiency of the two methods (100% vs. 94% with a *P*-value of 0.04), re-analysis of the data revealed that the difference was not statistically significant. Furthermore, their sample size was quite small, including only 68 women in both groups. In addition, like the first study, they did not measure the serum level of Beta-HCG before administrating contraceptive pills, which again could have led to miscalculation of the efficiency of the contraceptive methods.

In our study, however, we measured the serum levels of Beta-HCG both before and after the administration of the contraceptive pills. The participants were included only if the hormone level was negative before administration of the pills. In case the serum level of this hormone became positive after administration of each group of pills, they were considered as failure cases for that method.

Our sample size, however, was large enough for comparing side effects of the two regimens. For this purpose, 90 participants were needed in each group according to power calculations. Frequency and severity of side effects were, as it was expected, significantly higher among participants in HD group, especially in the case of nausea, vomiting, and dizziness, which is consistent with results of other studies. According to Task Force on Postovulatory Methods of Fertility Regulation (15), side effects of Levonorgestrel were reported to be significantly lower than those of Yuzpe regimen. This was also supported by another multicenter, double-blind, randomized controlled trial study (16). It is noteworthy that the considerably lower side effects of Levonorgestrel might be a reason for higher act of intercourse after drug administration in LNG group (due to better general status of women after drug administration in LNG group), resulting in higher pregnancy rate in this group and one reason for failure of the study to show

the expected greater efficacy of Levonorgestrel regimen.

Finally, in contrast with our expectations, change of menstrual bleeding pattern was quite the same for both groups (Table 5), which is in agreement with the results presented by lee et al. (16). Change occurs in spotting pattern due to administration of hormonal contraceptives is a challenging issue because its acceptability among women is highly culture- and religion-dependent (35). In the past, for example, women used to prefer regular menstrual cycles, whereas having less spotting cycles is more acceptable in the developed world (36). Or, less spotting cycles and even amenorrhea is more acceptable among white women compared to blacks (37). Therefore, since Iran is considered a religious country and change of spotting pattern can interrupt religious activities of Iranian women, use of ECPs should be assessed with respect to implications on menstrual cycle. A considerable body of evidence now exists, which supports greater efficiency of and milder side effects of Levonorgestrel compared to that of Yuzpe regimen. In Iran, however, Yuzpe is still the only emergency contraception method available. Therefore, it is recommended that Levonorgestrel be also available in Iranian governmental family planning centers for free and its use be encouraged by improving the level of knowledge among sexually active women as well as increasing and facilitating their access to it.

Conclusion

Complete knowledge and use of emergency contraceptive pills is quite low in Iran and further education as well as increased accessibility of ECPs is critical. Although patterns of menstrual bleeding was the same in both treatment groups, significantly fewer side effects of Levonorgestrel compared to those of Yuzpe regimen leads to greater acceptability of the former and can also be translated to greater efficiency. Therefore, it is recommended that Levonorgestrel be also available in Iranian governmental family planning centers for free so that it can gradually replace Yuzpe regimen.

Ethical Considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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