Nigerian Journal of Clinical Practice
December 2009 Vol. 12 (4):450-452

ASSESSMENT OF TWO EMERGENCY CONTRACEPTIVE REGIMENS IN IRAN: LEVONORGESTREL VERSUS THE YUZPE

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ABSTRACT

Objective: The purpose of this study was to compare the efficacy and tolerability of two emergency contraception (EC) methods, levonorgestrel versus the Yuzpe.

Methods: In a prospective, randomized, comparative study, we included 122 healthy volunteers who in the observed cycle had had only one act of unprotected intercourse within 72h of treatment. They were randomly allocated in levonorgestrol group (n=62) and Yuzpe (n=60). The levonorgestrel regimen consisted of two pills: 0.75 mg levonorgestrel, taken twice in the 12-h interval within 72h after unprotected intercourse. The Yuzpe method included two HD contraceptive pills taken as another regimen. Data were collected by questionnaire at first and 3 weeks later. The differences were compared with X^2&Fisher exact tests.

Results: There were no significant differences between two groups in any of the observed parameters. The levonorgestrel regimen was found superior to Yuzpe because it's more effectiveness (respectively 100% vs 91%, p=0.026) and fewer side effects.

Conclusion: The study showed more effectiveness and safety of the levonorgestrel regimen as emergency contraception. Thus we recommend levonorgestrel as an alternative EC method instead of the Yuzpe regimen in Iran or other developing countries in order to decrease unwanted pregnancy.

Key words: Yuzpe, Levonorgestrel, emergency contraception *(Accepted 5 November 2008)*

INTRODUCTION

Emergency contraception (EC) as a means to prevent unwanted pregnancies in special situations such as condom accidents, sexual abuse, and unprotected intercourse occurring around mid cycle, when there is a high probability of pregnancy. It is estimated that wider use of EC would greatly reduce the number of unwanted pregnancies and the number of abortions resulting from them[1].The most widely used emergency contraception (EP) methods in the world are the Yuzpe regimen (combined estrogen-progestin contraceptive pills) and the levonorgestrel (LNG) regimen (progestin only). The Yuzpe regimen was developed in 1980 and later compared to the LNG regimen in clinical trials. In the large randomized trial to date, the LNG regimen has been shown to be more effective and associated with fewer side effects than Yuzpe regimen[2]. The Yuzpe method of emergency contraception involves taking two doses of combined estrogen/progestin pills, with each dose containing 100µg of ethinyl estradiol and 500µg of evonorgestrel. The first dose is taken within 72h of unprotected coitus and the other is taken 12h later. The total regimen is therefore 200µg of ethinyl estradiol and 1 mg of levonorgestrel[3]. But levonorgestrel 0.75 mg is marked as two pills taken within 72h of unprotected coitus and the other is taken 12h later[4]. The most frequent women's complaint was nausea and vomiting [4]. Vomiting occurs in about 5.6% of women taking the LNG regimen compared to about 18.8% for the Yuzpe regimen. The management of vomiting shortly after taking EC is not well defined[1]. Ho and Kwan reported fewer side effects and better efficacy with levonorgestrel compared to the Yuzpe method[5].Several clinical studies have shown that combined emergency contraception pills (ECP) can inhibit or delay ovulation [6]. Some studies have shown histologic or biochemical alterations in the endometrium after treatment with the regimen, leading to the suggestion that EPCs may act by impairing endometrial receptivity to implantation of a fertilized egg[3]. Additional possible mechanisms include dysfunctional ovulation; interference with corpus luteum function; thickening of the cervical mucus resulting in trapping of sperm; alterations in the tubal transport of sperm, egg or embryo; and direct inhibition of fertilization[7,8]. No clinical data exist regarding the last three of these possibilities. The aim of this study was to compare the effectiveness between the Yuzpe and levenorgestrel regimens of EC in order to introduce safer and more effective method.

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STUDY DESIGN

One hundred twenty four healthy women volunteered for randomized comparative study measuring the effectiveness of two EC regimens from September 2006 to June 2007. The protocol was approved by the Shahid Sadoughi University Ethics Board and written informed choice was obtained from all participants. The comparison was focused on two regimens of postcoital contraception (PCC): the Yuzpe regimen and LNG. In the levenorgestrel group and the Yuzpe regimen group, 62 women were randomly allocated in each group. Randomisation was performed by the randomisation schedules. Having only

one act of unprotected intercourse within 72h of treatment in the observed cycle was study inclusion criteria. Reasons for exclusion included a history of irregular menstrual cycles, contraindications to hormonal contraception including imparted liver function, blood clotting disorders, family or personal history of venous thromboembolism or pulmonary embolism, intolerance to oral contraceptives and not to return for follow up visit. The levonorgestrel regimen consisted of two pills: 0.75 mg levonorgestrel taken twice in the 12h interval. The Yuzpe regimen consisted of two tables of ethynylestradiol 100μg and levonorgestrel 500μg taken twice in the 12h interval as well.

Finally, the medical history was taken and general examination and a pregnancy test were performed. All women were keeping a diary of the menstrual period and side effects, coitus protection with condom after the PCC in the same cycle and were asked to return for a follow-up visit one week after the expected menstrual period. The pregnancy was confirmed by a positive pregnancy test. Data were collected by Questionnaires that the study team completed them. The differences were compared with X^2&Fisher exact tests.

RESULTS

Demographic characteristics for the five subjects studied on the Yuzpe regimen and LNG regimen are provided in Table 1. There were no significant differences between the groups in any of the observed parameters. Two women were excluded from the study because they were lost to follow-up. Pregnancy occurred in five patients (8.3%) in the Yuzpe regimen, but no pregnancy occurred in the LNG (p=0.026) . In the Yuzpe group 60% of women and in the LNG group 62% of women reported normal and regular menses in the treatment cycle. But menstruation time was changed in 30% of women in the Yuzpe and 37% in the LNG group (Table.1). None of the observed women reported any change in the length or amount of bleeding.

There was no vomiting and necessity for substitute pill intake in the levonorgestrel group. Nausea, vomiting, headache and weakness were statistically less frequent. Otherwise a higher frequency of these parameters was observed in the Yuzpe group (Table.2).

Table 1**: Demographics for Subjects Studied on The Yuzpe Regimen and Levonorgestrol Regimen.**

Parameter	Yuzpe regimen (*n*=60) mean (SD)	Levonorgestrel (*n*=62)mean(SD	P_{value}[a]
Mean Age (years)	29.1(±7)	26.3(±6)	0.33
Gravid	3.03(±2.2)	2.4(±2.1)	0.118
Parity	2.8(±2.23)	2.3(±2.13)	0.18
Menstruation time with PCC			
Normal cycle vs. after treatment	36(60%)	39(62.09%)	0.945
Early menstruation	14(23.3%)	18(29.03%)	
Late menstruation	5(6.6%)	5(8.06%)	
Interval between coitus and PCC(h)	7.9(±8.01)	11.6(±13.3)	0.065

Early mensturation is occurance of mensturation earlier of normal periods for the same woman.

Late Mensturation is occurance of mensturation later than normal periods for the same woman.

PCC: Post coital contraception;
SD: Standard deviation;
a: If P_{value} was less than 0.05, there was significant differnce between two parametr

Table 2: **Incidence of Complaints after Postcoital Intake of Each Regimen (%).**

Complications	Yuzpe Group (n=60)	LNG Group (n=62)	P_{value}
Nausea	68.3	6.5	0.000
Vomiting	25	0	0.000
Headache	21.7	0	0.000
Weakness	16.7	1.6	0.004
Hot flash	6.7	3.2	0.436

DISCUSSION

We evaluated two regimens of PCC: levonorgestrel and Yuzpe regimens in a prospective, randomized, comparative study. Concerning baseline subjects, the patients in both groups were similar. We observed that pregnancy occurred in five patients (8.3%) in the Yuzpe regimen, but no pregnancy occurred in the LNG (p=0.026).Wilcox has calculated the probability of conception to range from 10%, when intercourse occurs five day before ovulation, to 33%, when it occurs on the day of ovulation itself[9]. Pretnar-Darovec et al showed that no pregnancies occurred in their study of the WHO multicenter trial. They are aware of the fact that this may be due to the small number of observed cycles [4]. Ho et al compared the Yuzpe and levonorgestrel regimen and found that the pregnancy rate was 3.5% in the Yuzpe regimen compared to 2.9% in the LNG regimen [5]. The best evidence showed that the proportion of pregnancies prevented(compared with the expected number without treatment) is about 85% for the LNG regimen compared to 57% for the Yuzpe regimen[10]. A meta analysis of eight studies including the WHO study of 1998(Task Force 1998) concluded that when used within 72h of coitus, the Yuzpe regimen prevents about 74% of expected pregnancies[11]. Our results may be due to a small number of observed cycles.Pregnancy rate has been shown to be inversely related to the time the pill was taken after intercourse [10]. In most cases enrolled in our study, the interval between intercourse to take pill was less than 24h. Our study agrees with the conclusions drawn from the entire WHO trial that the pill should be taken as soon as possible after unprotected intercourse. There is concern about decreased absorption and contraceptive effectiveness subsequent to vomiting shortly after taking EC[12,13].

Gynaecologists practice Bulletin on emergency oral contraception showed that "there is no evidence on which to base a recommendation for repeating the dose if emesis occurs. But it seems reasonable to infer that if gastrointestinal symptoms are estrogen mediated secondary to an effect on the central nervous system, absorption of the dose should have occurred by the time of emesis"[14]. There was no significant changes in the menstrual cycles after these regimens. The side effects of both regimens were assessed. The differences in side effects between two groups were statistically significant and similar to those of other studies [4]. Yuzpe reported that nausea occurred in up to 50% of cases [15].The women in our Yuzpe group experienced nausea in 68.3% and vomiting in 25%.These side effects were less frequently after levenorgestrel regimen.

CONCLUSION

The study showed more effectiveness and safety of the levonorgestrel regimen as emergency contraception. We recommend the use of levonorgestrel as an alternative EC method instead of the Yuzpe regimen as soon as possible in Iran or other developing countries in order to reduce the prevalence of unwanted pregnancy.

ACKNOWLEDGEMENT

The authors would like to thank the study counsellors Professor Abass Aflatonian, Dr Ali Babaei and the women who participated in the trial.

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