J. of Obst. & Gyn. of India Vol. 52, No. 2 : March/April 2002 Pg 108-111

Emergency Contraception : A Randomized Controlled Trial of Levonorgestrel Versus Yuzpe Regimen – Indian Experience

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Summary

Offering emergency contraception is an important family planning measure. Several methods have been described. In the present double blind, randomized controlled trial a comparison has been done between Yuzpe method and Levonorgestrel alone for emergency contraception. Both methods have been used within 72 hours of unprotected intercourse. Two women conceived following Yuzpe method, while no pregnancies occurred after Levonorgestrel course. Observed reduction in the number of expected pregnancies is 71% with Yuzpe method and 100% with Levonorgestrel. Significantly more side effects occurred after use of Yuzpe method. The effect on menstrual cycle and bleeding pattern was similar in the two groups.

Introduction

Demand and use of effective methods of contraception is gradually increasing, still women often require emergency contraception as a 'fall back' method to avoid unwanted pregnancy after unprotected sexual intercourse or following failure of their usual method of contraception. Several methods have been used in such emergencies. Yuzpe et al (1974) evaluated a combination of 0.1 mg ethinyl estradiol and 1 mg norgestrel given in two doses 12 hours apart. Though effective, substantial side effects are reported with its use. Subsequent WHO supported trial using pure progesterone levonorgestrel in two doses of 0.75 mg taken 12 hours apart was found to be effective when used upto 48 hours after sexual exposure with significantly fewer side effects (HO and Kwan, 1993). To compare Yuzpe method with levonorgestrel for emergency contraception, a double blind randomized controlled trial has been carried out by WHO (1998) in 21 centres across the world. Both methods have been used upto 72 hours following unprotected intercourse. We are reporting on the Indian component of this multicentre trial.

Material and Methods

This is a prospective study which recruited women in 21 centres for emergency contraception. Ours was only centre from India participating in this study. Women were randomized in two groups. As randomization was double blind neither the recipient nor the doctor was aware of the method used. We recruited 100 women who requested for emergency contraception (EC) within 72 hours of a single unprotected coitus. Fifty women received 2 doses of 0.75 mg. evonorgestrel 12 hours apart and 50 received 100ug ethinyl estriadiol and 0.5 mg levonorgestrel repeated 12 hours later. Only women having regular menstrual cycles and willing to abstain from further intercourse till next period were included. Women who were breast feeding, had used hormonal method of contraception, were unsure about date of last menstrual period or were

incapable of maintaining a menstrual diary were not recruited.

After obtaining an informed consent all women were given 2 identical tablets (2 tablets of 0.05 mg ethinyl estradiol and 0.25 mg levonorgestrel or 1 tablet of 0.75 mg levenorgestrel plus one placebo tablet). The first dose was given in the clinic and women were asked to take second dose 12 hours later. One additional dose was given to be used if vomiting occurred within 4 hours of either dose. No antiemetics were given. All women were told to abstain from further sexual activity till the onset of next period or use condom if sex was inevitable. They were given diary cards to record side effects, vaginal bleeding/spotting and further acts of intercourse till follow up visit. Follow up was scheduled 1 week after the expected date of next menstrual period. If menstruation has not started till this time a urine pregnancy test was done and women were managed appropriately

Outcome Measure

After decoding the double blinding, the results in the two groups were compared statistically. The primary outcome measure was occurrence of unintended pregnancy following use of emergency contraception. As overall pregnancy rates can be quite misleading, the expected number of pregnancies by timing of coitus in relation to predicted ovulation day were calculated in both groups by using method described by Dixon et al (1980). Estimated reduction in expected pregnancies was compared in the two groups.

Secondary outcome measures included occurrence of side effects and alterations in menstrual cycle and bleeding pattern.

Results

A total of 100 women were enrolled. Though 57% women had used a method of contraception in the past, in the cycle necessitating use of EC 87% had unprotected intercourse, while 13 subjects were recruited following a possible condom failure The base line characteristics of these women are summarized in table I. Demographic characteristics were similar in the two groups. Seventy five women were parous, 13 and 9 women have had previous spontaneous and induced abortions respectively with 5 women having more than 2 abortions. No women had previous molar or ectopic pregnancy. The request for EC was made within 12 hours of sexual exposure by 12 subjects, between 12-24 hours by 24, between 24-48 hours by 41, between 48-72 by 23 women. The reporting time was similar in the two groups (Table I). The longest interval between EC use and intercourse was 70.5 hours. Women reporting more than 72 hours later were not recruited.

Two women conceived and both had intrauterine pregnancies. One elected to have medical termination of pregnancy, another continued pregnancy and delivered at term a healthy female baby weighing 2.7 kg with no congenital malformations. Both pregnancies occurred in women using Yuzpe method.

Women had reported from -9 to +10 cycle day as calculated from ovulation day. The day of ovulation was calculated by subtracting 14 days from the first day of next expected period estimated by usual menstrual cycle length. The probability of pregnancy varies considerably by coital day in relation to time of ovulation. On calculating the probability by cycle day it was estimated that 8 pregnancies would have occurred in levonrogestrel group and 7 in Yuzpe group if

Table I
Baseline Characteristics of subjects

		Yuzpe regimen n = 50	Levonorgestrel n = 50	Total n = 100
Mean Age (Years)		28.3	27.9	28.0
Parity	0	13	12	25
	1-3	33	35	68
	> 3	4	3	7
Mean weight (Kg)		52.3	53.1	-
Mean height (cm)		152.6	152.9	-
Mean cycle length (days)		29.6	30.1	-
Delay in treatment	< 12 hrs	5	7	12
	< 24 hrs	13	11	24
	25-48 hrs	19	22	41
	> 48 hrs	13	10	23

contraception was not used. There was 100% reduction in estimated number of pregnancies in levonorgestrel group (0/8) and 71% (2/7) in Yuzpe group (Yuzpe et al, 1974)

A comparison of the side effects in the two groups revealed that levonorgestrel was better tolerated than Yuzpe method (table II). Nausea, vomiting, headache, dizziness and fatigue were less common with levonorgestrel. One woman in Yuzpe group required an extra dose due to vomiting.

Table II
Side effects of Emergency Contraception

	Yuzpe n = 50	LNG n = 50	Total n = 100
Nausea	3	1	4
Vomiting	3	2	5
Headache	5	6	11
Dizziness	1	1	2
Fatigue	7	5	12
Breast tenderness	1	-	1
Low abdomen pain	4	2	6
Diarrhoea	-	-	-
Total	24	17	41

Table III
Effect of Emergency Contraception on menstruation

	Yuzpe n = 48	LNG n = 50	Total n = 98
On time	33	38	71
Delay 3-7 days	6	4	10
Delay > 7 days	2	3	5
Early 3-7 days	5	3	8
Early > 7 days	2	2	4
Blood loss			
Similar	36	29	65
Less	5	9	14
More	7	12	19

The effect on menstrual cycle was similar in the two groups (Table III). Two women in Yuzpe group conceived. Of the remaining, 71 women had return of menses within 3 days of expected date, 5 had delay of more than 7 days, 10 between 3-7 days, 8 had earlier onset by 3-7 days and 4 had periods more than 7 days earlier. The longest delay was 26 days and earliest period came 22 days before the expected date. Amount of menstrual blood loss as estimated by the patient was similar to normal in 65, more than normal in 19 and less in 14. None of the patient's experiencing more than normal blood loss required any intervention. There was no statistical difference in the bleeding pattern in the two groups.

Discussion

The aim of emergency contraception is to avoid an unwanted pregnancy without causing any side effects. Yuzpe regimen, the most common method for emergency contraception (Trussel et al. 1996) can prevent upto 75% of pregnancies that would occur if no treatment was taken, but is associated with vomiting in 20% and nausea in 50% women (Ho & Kwan, 1993). In our study, 2 pregnancies occurred in 50 women using Yuzpe method. When calculated according to Dixon et al (1980) by menstrual cycle day 7 pregnancies were expected to occur in them, thus there was 71% reduction. In our series no pregnancy occurred in 50 women receiving 2 doses of levonorgestrel starting within 72 hours of sexual exposure. On calculation by menstrual cycle day, 8 pregnancies were expected in these women. Thus levonorgestrel was found to be more effective when used as an emergency contraceptive.

Results of multicentre trial by WHO (1998) also revealed a greater efficacy of levonorgestrel in comparison with Yuzpe method, both in terms of crude and adjusted pregnancy rates and pregnancies prevented. The crude pregnancy rate was 1.1% (11/976) in Levonorgestrel group and 3.2% (31/979) in Yuzpe regimen group. The proportion of pregnancies prevented was 85% with levonorgestrel and 57% with Yuzpe regimen (WHO 1998). Besides greater efficacy, the levonorgestrel regimen was also better tolerated than the Yuzpe regimen both in Indian women as well as in the total series. Nausea (23.1 vs 50.5%) and vomiting (5.6 vs 18.8%) were significantly less frequent with levonorgestrel than Yuzpe regimen.

Study by HO and Kwan (1993) revealed a pregnancy rate of 3.5% with Yuzpe regimen and 2.9% with levonorgestrel. A comparative study on use of levonorgestrel alone used upto 48 hours of unprotected intercourse showed it to be slightly less effective with significantly less vomiting (2.7% vs 22.4%). Neither regimen had any substantial effect on menstrual cycle. Trials comparing Yuzpe regimen with mifepristone (Glasier et al, 1992) revealed a significant delay in onset of next period following use of mifepristone.

Conclusion

As levonorgestrel alone was associated with higher efficacy and fewer side effects, it is recommended that this should replace Yuzpe method as a standard regimen for emergency contraception.

Acknowledgement

"This investigation received financial support from the UNDP/UNFPA/WHO/World Bank, Special programme of Research, Development and Research Training in Human Reproduction, World Health Organization.

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