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Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians

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Abstract

Emergency contraception was introduced in Nigeria over two decades ago, but few women have used this method even in emergency situations because of the side effects. To find an acceptable levonorgestrel regimen for emergency contraception in our community, the two-dose regimen 0.75-mg levonorgestrel 12 h apart (group A) and the single dose 1.5-mg levonorgestrel (group B) were studied in 1118 volunteers. Mild side effects such as nausea, vomiting, lower abdominal pains, menorrhagia, dizziness, headache, and breast tenderness were reported. Significantly more women in the high-dose group reported headache, breast tenderness, and heavy menstrual flow. Eleven pregnancies (1.0%) were reported (7 in group A and 4 in group B). The crude relative risk of pregnancies was similar in the two groups (RR = 9.71, 95% CI = 0.32–1.55; $p > 0.05$). On the other hand, the estimated effectiveness rate of 86.80% in group A was significantly lower than the 92.99% for group B ($p < 0.05$). The pregnancy rates increased with delay in starting treatment and if further acts of unprotected sexual intercourse took place after treatment. It was concluded that both regimens were effective and safe. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Emergency contraception; Levonorgestrel; Safety; Effectiveness; Nigerians

1. Introduction

The problems of preventing and caring for complications of unwanted pregnancies in Nigeria, especially among the youth, continue to generate great concern in various reproductive health management circles [1–4]. The overall contraceptive prevalence rate in the country is less than 20%, and many youths who are at high risk of unwanted pregnancies are not using effective contraceptive methods [4,5]. Instead, they prefer to induce abortions as a means of preventing early motherhood [6,7]. These illegally induced abortions are performed by poorly trained personnel in secrecy with attendant risk of sepsis, hemorrhage, organ damage, and death [1,2,8,9].

To satisfy the unmet contraceptive needs of the youth in the country, various workers have highlighted the role of emergency contraception [5,10]. Although emergency contraception implies a device not to be used routinely but in emergency situations [11], the method is helpful to youths that engage in sporadic, unplanned, and unprotected sexual intercourse [5].

The two readily available methods of emergency contraception in Nigeria are the Yuzpe regimen, using combined high dose of estrogen and progesterone [12], and the levonorgestrel pill [13]. These pills are obtainable without prescription. Reports have suggested that levonorgestrel preparations are better tolerated and more effective than the Yuzpe regimen [13,14]. The latter is associated with nausea, vomiting, and fatigue that are likely to affect its acceptability and effectiveness [13–15]. On the other hand, levonorgestrel-only pills cause anxiety from delay in return of menstruation and more bleeding problems than the Yuzpe regimen, although these side effects are rare when used strictly for emergency contraception [13,14]. Both regimens are given twice, 12 h apart, within 72 h of sexual exposure during the ovulation period for those who desire them. Unfortunately, despite their ready availability, these pills are rarely used by the youth even in emergency situations [16]. This is because of the fear of side effects by the youth [5] and the reluctance by health workers to prescribe them [10]. In fact, experience in our unit has shown that some clients would take only the initial dose and default as a

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result of fear and accompanying side effects. This limits the efficacy of the regimens.

Recently, we noticed that a few of our clients would take the two levonorgestrel doses at once without major adverse effects or accidental pregnancies. Therefore, we designed a prospective study to compare the efficacy and safety of the standard regimen of levonorgestrel pills (i.e., 1.5 mg in two split doses taken 12 h apart) with 1.5 mg levonorgestrel taken once for emergency contraception. This article presents our findings.

2. Participants and methods

The participants in this study were healthy noncontracepting women in the reproductive age group who requested emergency contraception, having been sexually exposed within 72 h of presentation at the family planning clinic, University College Hospital, Ibadan, and Planned Parenthood Federation of Nigeria (PPFN), Ikolaba, Ibadan. They were recruited if they had regular menstrual cycles of 21–35 days, had intercourse during the ovulation period, and gave informed written consent for participation in the study. Those who were not available for follow-up, were pregnant, or had contraindications to the use of hormonal contraceptive pills were excluded.

The study was double-blind, and participants were randomized into two groups (A and B) using a computer-generated random table. The medications were packed in similar boxes, each tagged with the user's name, and containing two tablets. Group A took the box containing one 0.75 mg levonorgestrel tablet and one similarly-looking, inactive placebo tablet, taken twice 12 h apart. Group B took two 0.75 mg levonorgestrel tablets (i.e., 1.5 mg levonorgestrel) at presentation and two placebo tablets 12 h later. These were administered by a family planning nurse who was blind to the contents in the boxes. Those who vomited within 4 h of taking their medication had their last medication repeated.

After treatment, each participant was advised to abstain from further acts of sexual intercourse until menstruation ensued (compliance with this instruction was not enforced) and to keep a calendar of events such as vaginal bleeding or spotting, coitus, cycle-day at presentation, vomiting, and others. Follow-up was continued until menstruation occurred, with home visits in the case of a default.

2.1. Statistical analysis

The sample size was determined according to the method described by Kirkwood [17] using the failure rate of 1.1% for levonorgestrel contraceptives (P_1) and 7% without the use of postcoital contraceptives (P_0). These figures have been used in previous reports [18,19]. With $Z_a = 1.96$, $Z_b = 1.28$, $p = (P_1+P_0)/2$ at statistical power of 90%, the required minimum sample (n) for each group was calculated to be 543 using the formula:

$$n = \left[\frac{Z_A\sqrt{2P(1-P)} - Z_B\sqrt{P_1(1-P_1)+P_0(1-P_0)}}{(P_1-P_0)}\right]^2$$

Deliberate oversampling was carried out to allow for defaulters. All entries were made on a data card, and computer analysis was performed using Epi Info version 6.02 (CDC/WHO, Georgia, USA). Analysis was by intention to treat. Frequency tables were generated and means ± SD was compared using analysis of variance. Pregnancy rates and crude relative risks with 95% confidence interval were compared by standard methods. The expected number of pregnancies in each group was estimated by multiplying the number of women having unprotected coitus on each day of the menstrual cycle by the probability of conception on each cycle day and the estimated reduction in expected pregnancies calculated. Also, the effectiveness of each regimen was calculated using the method developed by Trussell et al. [20]. The day of ovulation was estimated by subtracting 14 days from the expected date of the next period.

Table 1
Admission characteristics of the subjects in each group

Characteristics	Levonorgestrel regimen A group (n = 545)	Levonorgestrel regimen B group (n = 573)
Mean age ± SD (yrs)	27.4 ± 7.0	26.6 ± 7.2
Mean body mass index ± SD (kg/m^2)	26.1 ± 3.5	25.8 ± 3.7
Mean menstrual cycle length ± SD (days)	28.8 ± 2.6	28.5 ± 2.7
History of ≥1 previous pregnancy	66.1%	59.3%
Use of emergency contraception	39.4%	34.9%

3. Results

The study consisted of 1160 women, with 560 women in group A and 600 in group B. Of these, 42 women (3.6%) were completely lost to follow-up and were withdrawn from final analysis. Of the 1118 women (96.4%) analyzed, 545 women were in group A and 573 women were in group B. Only 1062 subjects (518 in group A and 544 in group B) provided enough information to be assessed for side effects and timing of next menses.

3.1. Admission characteristics/timing of coitus and treatment

The women in the two groups had similar admission characteristics (Table 1). About 33% of the women had used emergency contraceptives in the past, and over 50% of them had had a previous pregnancy that ended in an abortion or

Table 2
Side effects reported by women who gave complete information in each group

Side effects.	Group A, % (n = 518)	Group B, % (n = 544)
Nausea	22.9	24.3
Vomiting	8.4	7.8
Dizziness	13.9	12.6
Headache	14.5	21.3*
Breast tenderness	8.8	12.9*
Lower abdominal pains	18.3	15.6
Heavy menses	10.5	15.5

* Significant difference ($p < 0.05$).
Some users reported more than one side effect.

a live birth. Among the women in group A, 255 (46.7%) had coitus more than one day before the ovulation day, 172 (31.6%) between one day before and one day after the ovulation day, and 118 (21.6%) more than one day after the ovulation day. The corresponding number of women in group B were 280 (48.9%), 185 (32.3%), and 108 (18.8%), respectively. Thus, the timing of coitus relative to expected ovulation day was similar in the two groups. The timing of postcoital contraception relative to the time of expected ovulation was also similar in the two groups. Treatment started within 24 h for 60% of the women (320 in group A and 390 in group B), between 24 h and 48 h for 30% of the women (190 in group A and 210 in group B), and after 48 h for 10% of the women (35 in group A and 53 in group B).

3.2. Events occurring after treatment

The side effects observed after treatment were nausea, vomiting, dizziness, headache, breast tenderness, lower abdominal pain, and menorrhagia (Table 2). Women in group A had more vomiting, dizziness, and lower abdominal pain, and less nausea, headache, breast tenderness, and increased menstrual flow than those in group B. Significant differences ($p < 0.05$) were seen for headache, breast tenderness, and heavy menstrual flow only (Table 2).

Menstruation resumed after a similar interval in the two groups (Table 3). It was early (>7 days before expected menses) for about 25% of the women, unchanged for 20%, and delayed (>7 days after expected menses) for 18%. Areas of significant differences are shown on Table 3.

Table 3
Time of resumption of menstruation after treatment in each group

Day of onset of period relative the expected 1st day of period	Group A, % (n = 545)	Group B, % (n = 573)
<−7 days	29.9	19.9*
−7 to −4 days	14.9	14.8
−3 to +3 days	25.5	30.4*
+4 to +7 days	9.9	9.9
>+7 days	14.9	19.9*
No information	4.9	5.1

* Significant difference ($p < 0.05$).

3.3. Failure of regimen

Eleven intrauterine pregnancies (7 in group A and 4 in group B) were recorded (Table 4). There were no ectopic pregnancies. Three women in group A and one in group B continued with their pregnancies and delivered live healthy babies, while the others were lost to follow-up. The pregnancy rate in group A was 1.28% (0.34–2.2, 95% CI) and in group B was 0.69% (0.02–1.38, 95% CI). There was no significant difference in the crude relative risk of pregnancy in the two groups (RR = 0.71; 0.32–1.55, 95% CI; $p > 0.05$). The relative risk of pregnancy in group A compared to group B increased from 0.68 (0.14–3.36, 95% CI) for ≤24 h delay in treatment to 0.82 (0.30–2.23, 95% CI) for 49–72 h delay in treatment. The relative risk of pregnancy for a delay between 24–48 h before treatment was 0.47 (0.09–2.59, 95% CI). These differences were not significant ($p > 0.05$). Further acts of sexual intercourse increased the pregnancy rates in each of the two groups (1.7% vs. 1.1% in group A, and 1.1% vs. 0.5% in group B). Analysis of the prevented fraction (1 - observed pregnancies/expected pregnancies) gave results that were conclusively similar to those for pregnancy rates.

The estimated effectiveness rate using the British, North Carolina, and pooled conception probabilities by cycle day were as shown in Table 4. With the British conception probabilities, the effective rate was 87.53% (73.00–94.24%, 95% CI) for regimen A and 93.39% (82.03–97.57%, 95% CI) for regimen B. With North Carolina conception probabilities, regimen A had an effectiveness rate of 89.36% (77.11–96.06%, 95% CI) for all conceptions and 84.09% (65.78–92.60%, 95% CI) for recognized conceptions. The corresponding effectiveness rates for regimen B were 94.14% (84.16–97.84%, 95% CI) and 91.52% (77.07–96.86%, 95% CI), respectively. The effectiveness rates for the two regimens using the conception probabilities for all conceptions and recognized conceptions calculated from pooled British and North Carolina data are as shown in Table 4. These results indicated that regimen A was significantly less effective than regimen B ($p < 0.05$). Both drug regimens were effective the earlier they were taken before ovulation.

4. Discussion

This study shows that the levonorgestrel regimens in both groups A and B are effective for emergency contraception with minimal side effects. Their effective rates were better than those of combined estrogens and progestins, judging from reports of previous trials [12,13,21]. The regimen for group B appears more effective than that for group A, not in terms of raw pregnancy rate or relative risk but in

Table 4
Comparative estimated effectiveness rates of Groups A and B regimens

Day	Cycles	Pregs		British	NC-ac	NC-rc	Pooled-ac	Pooled-rc
Levonorgestrel Regimen A								
−7	70	0	Observed pregs	7	7	7	7	7
−6	29	0	(var)	6.71	6.71	6.71	6.71	6.71
−5	30	0	Expected pregs	56.15	65.80	43.99	61.49	53.05
−4	32	0	(var)	58.60	69.22	30.45	31.40	26.76
−3	44	0	Effectiveness rate	87.53%	89.36%	84.09%	88.62%	86.80%
−2	50	0	(var)	0.00242	0.00173	0.00386	0.00188	0.00255
−1	57	0	Lower 95% limit	73.00%	77.11%	65.78%	75.98%	72.07%
0	61	2	Upper 95% limit	94.24%	95.06%	92.60%	94.61%	93.77%
1	54	3						
2	32	1						
3	35	1						
4	51	0						
Total	545	7						
Levonorgestrel Regimen B								
−7	73	0						
−6	32	0						
−5	35	0	Observed pregs	4	4	4	4	4
−4	39	0	(var)	3.88	3.88	3.88	3.88	3.88
−3	48	0	Expected pregs	60.55	68.31	47.16	65.20	57.05
−2	53	0	(var)	66.70	71.46	33.05	34.19	30.02
−1	63	0	Effectiveness rate	93.39%	94.14%	91.52%	93.87%	92.99%
0	54	2	(var)	0.00114	0.00088	0.00185	0.00094	0.00124
1	65	1	Lower 95% limit	82.03%	84.16%	77.07%	83.63%	81.25%
2	35	1	Upper 95% limit	97.57%	97.84%	96.86%	97.70%	97.38%
3	35	0						
4	40	0						
Total	573	4						

terms of effectiveness rate, which is more relevant in assessing the effectiveness of emergency contraceptives [20]. This result may be different if those women lost to follow-up became pregnant and were considered. For example, if no pregnancy occurred among the 15 women who were withdrawn from analysis in group A and at least 5 pregnancies occurred among those withdrawn in group B, the result would not be significant. Other examples of extreme cases with a reversal of the effect are no pregnancy among the 15 women lost to follow-up in group A and at least 12 pregnancies or at most 27 pregnancies among those lost to follow-up in group B. Conversely, in the best-case scenario (i.e., no pregnancy in all those lost to follow-up), the result would be identical to our findings.

The earlier either levonorgestrel regimen was given following sexual intercourse, the greater its efficacy. This influence of timing of treatment on the efficacy of emergency contraceptives has been reported in studies elsewhere [22]. As in the WHO study [22], an inverse relationship between the efficacy of treatment regimens and the time of treatment following unprotected sexual intercourse was seen in the present study. The clustering of pregnancies around predicted ovulation validates the concept of conception probabilities in this study. In view of the biologic variability in cycle length and the need to rely on calculated estimates of the day of ovulation, the occasional pregnancies following intercourse outside the fertile period is to be expected. Our low pregnancy rates with the two regimens are comparable with the rates quoted for levonorgestrel trials in studies elsewhere [13,22,23]. The variables that were likely to affect the pregnancy rates in this study include the distribution of the timing of intercourse with respect to ovulation among the participants, the proportion of women in the less fertile age groups, and the proportion that had unprotected sexual intercourse as opposed to failure of the barrier method being used.

Side effects from the contraceptives are very likely to affect their acceptability by users. The group B women who took a larger dose of levonorgestrel at once suffered from headaches, breast tenderness, and menorrhagia more than those in group A. These side effects are features of progesterone-only contraception that are dose-dependent and are, therefore, not surprising. The side effects encountered in both groups were similar to those reported in the WHO trial in 1998 [13] and have been shown to be unrelated to the number of levonorgestrel tablets taken but varied markedly between regions. It seems that strength of a single dose of levonorgestrel tablets has influence on some of the side effects and individual reactions to the regimens are quite important. However, it is reassuring that the side effects encountered in this study were minimal and did not have a lasting effect on the individuals. Thus, they are unlikely to

prevent the use of either regimen for emergency contraception among those who need protection from unwanted pregnancies. We reported a delay in return of menstruation beyond 7 days in 195 women in this study. Such delays can be worrisome to some women who are already concerned about the possibility of an unintended pregnancy. Therefore, information about this important event is essential when counseling potential users.

In conclusion, both regimens of emergency contraception evaluated in this study are effective, with the single 1.5 mg levonorgestrel (regimen B) appearing more effective than the split doses of 0.75 mg taken twice 12 h apart (regimen A). However, acceptable minor inconveniences were encountered with regimen B. The earlier each regimen is given after unprotected sexual intercourse, the more the efficacy. These two regimens will add to the contraceptive armamentarium of our clientele, especially the youth. The choice of which regimen to use will depend on various factors that include the client's choice and her motivation to repeat a second dosage.

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