



Original research article

Effect on pregnancy rates of the delay in the administration of levonorgestrel for emergency contraception: a combined analysis of four WHO trials[☆]

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Abstract

Background: Levonorgestrel is an effective method for emergency contraception (EC) and is used worldwide. Consistent with its mechanism of action in delaying ovulation, the earlier it is administered within 72 h of an unprotected act of intercourse, the more effective it is. There is uncertainty, however, about its effectiveness after 72 h. This analysis explores the effect of 24-h intervals of delay in levonorgestrel administration on pregnancy rates when used until 120 h of an unprotected act of intercourse.

Study Design: Data were analyzed from 6794 women participating in four World Health Organization randomized trials and receiving 1.5 mg of levonorgestrel for EC in a single dose or split into two doses 12 h apart, within 48, 72 or 120 h of an act of unprotected intercourse. The pregnancy rates among women in successive days after an unprotected act of intercourse and odds ratios of pregnancy were calculated using logistic regression with the first day as the reference.

Results: For the four trials combined, odds ratios for pregnancy in the second, third and fourth day with respect to the first day were not significantly different from 1 at the 5% level of significance. On the fifth day, the odds ratio of pregnancy compared to the first day was almost 6.

Conclusions: Levonorgestrel for EC should be administered as soon as possible after unprotected intercourse. Delaying levonorgestrel administration until the fifth day after unprotected intercourse increases the risk of pregnancy over five times compared with administration within 24 h. It is uncertain whether levonorgestrel administration on the fifth day still offers some protection against unwanted pregnancy. © 2011 Elsevier Inc. All rights reserved.

Keywords: Emergency contraception; Levonorgestrel; Effectiveness in successive days; Combined analysis; Meta-analysis

1. Introduction

Levonorgestrel has been shown to be more effective than the Yuzpe regimen for emergency contraception (EC) and to have a better side-effect profile [1]. Its effectiveness has been assessed when administered within 120 h of an unprotected act of intercourse [2,3]. It has been shown that the earlier

these regimens are administered within 72 h of an unprotected act of intercourse, the more effective they are [4]. Although there had been some evidence of decreasing effectiveness of levonorgestrel (LNG) beyond 72 h [2], the extent and time pattern of this decrease between 72 and 120 h remained unclear. Combination of results from two World Health Organization (WHO) trials [1,2] provided some evidence of effectiveness until the fourth day following an unprotected act of sexual intercourse [5]. By combining data from four WHO trials [1–3,6], including one recently published [3], we sought to accrue a larger number of women in each of the successive days after an unprotected act of intercourse to increase the power for the estimation of the relationship between delay in administration and effectiveness in 24-h intervals.

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2. Materials and methods

The present article combines data from 6794 women participating in four WHO randomized trials and receiving 1.5 mg of LNG for EC in a single dose or split into two doses 12 h apart, within 48 h [6], 72 h [1] or 120 h [2,3] of an act of unprotected intercourse. All four studies were randomized controlled trials, randomization being applied to different EC regimens. The description of studies is shown in Table 1.

The proportions of women becoming pregnant (from now on denoted as pregnancy rates) among those recruited and receiving LNG in successive days after an unprotected act of intercourse were calculated for each trial and for all the trials combined. When there were two LNG regimens included in the trial [2,3], the two regimens were combined based on their similarity regarding efficacy and safety outcomes. The odds ratios (OR) of pregnancy for each of the successive days of delay after an unprotected act of intercourse, for the four trials combined, were calculated using logistic regression and the first day as reference. This analysis was repeated using RevMan [7] with a fixed model and the inverse variance method, but results are not presented since they were very similar to the ones obtained using logistic regression. The I^2 statistic was calculated to assess heterogeneity, and the homogeneity of the effect of delay across trials was tested by the interaction delay by trial in a

logistic regression model. This technique was also used to adjust for baseline variables for the two oldest trials [1,2] since the day of delay was not randomized and might be subject to confounding bias.

3. Results

The number of women recruited and allocated to a LNG arm in the four trials was 7219. The number in the efficacy populations in LNG arms in the four trials was 6921, and the number of women with data on time interval between intercourse and treatment and analyzed for delay was 6794 (see Table 1 for these data by trial). There was a significant effect of delay on the proportion of women who became pregnant ($p < .0001$). The pregnancy rate varied between 0.7% (14/2065) and 1.6% (17/1059) during the first 4 days (96 h) after unprotected intercourse and increased to 5.2% (12/230) on the fifth day (Table 2). The ORs for pregnancy on the second, third and fourth day with respect to the first day were not significantly different from 1 at the 5% level. They were, respectively, 0.68 (95% CI 0.36 to 1.28), 1.74 (95% CI 0.94 to 3.19) and 0.87 (95% CI 0.26 to 2.89). On the fifth day (96–120 h), the OR of pregnancy compared to the first day was almost 6 (OR=5.81, 95% CI 2.87 to 11.76) (Fig. 1) and the percentage of women who became pregnant

Table 1
Characteristics of WHO EC trials using LNG

Trial	Interventions	Participants requesting EC within	Centers	Sample size and number analyzed for delay
Randomized controlled trial of LNG vs. the Yuzpe regimen of combined oral contraceptives for EC [1]	1. LNG 0.75 mg repeated 12 h later 2. Yuzpe regimen (ethinyl estradiol 100 mcg plus LNG 0.5 mg) repeated 12 h later	72 h	21 centers in 14 countries	1998 total LNG: 1001 Yuzpe: 997 974 in the LNG regimen analyzed for delay (97.3%)
Low-dose mifepristone and two regimens of LNG for EC: a WHO multicenter randomized trial [2]	1. 10 mg single-dose mifepristone 2. 1.5 mg single-dose LNG 3. Two doses of 0.75 mg LNG given 12 h apart	120 h	15 centers in 10 countries	4136 total Mifepristone: 1380 Single-dose LNG: 1379 Two-dose LNG: 1377 Total LNG: 2756 2695 in the LNG regimens analyzed for delay (97.8%)
A prospective randomized comparison of LNG with the Yuzpe regimen in post-coital contraception [6]	1. LNG 0.75 mg repeated 12 h later 2. Yuzpe regimen (ethinyl estradiol 100 mcg plus LNG 0.5 mg) repeated 12 h later	48 h	One center in Hong Kong	880 total LNG: 440 Yuzpe: 440 331 in the LNG regimen analyzed for delay (75.2%)
A randomized, double-blind study to compare two regimens of LNG for EC in Nigeria [3]	1. 1.5 mg single-dose LNG 2. Two doses of 0.75 mg LNG given 12 h apart	120 h	7 centers in Nigeria	3022 total Single-dose LNG: 1510 Two-dose LNG: 1512 Total LNG: 3022 2794 in the LNG regimen analyzed for delay (92.5%)

Design: Prospective multicenter randomized controlled trials (random assignment of interventions to subjects within centers).

Participants: Healthy women with regular menses, not using hormonal contraception, requesting EC within 48, 72 or 120 h (depending on the trial) of an unprotected act of intercourse.

Main outcome: Pregnancy.

Table 2

Number of pregnancies, number of women and pregnancy rates (%) by 24-h intervals of delay between an unprotected act of intercourse and administration of LNG, and ORs of pregnancy for intervals after 24 h with respect to the first 24 h, with 95% CIs, for four WHO studies and for the combined data

Study	Delay (h)	No. of pregnancies	No. of women	Pregnancy rate (%)	OR (95% CI)
WHO 1998 [1]	0–24	2	450	0.4	1 (Ref)
	25–48	3	337	0.9	2.00 (0.33–12.11)
	49–72	5	187	2.7	6.02 (1.18–32.01)
WHO 2002 [2]	0–24	20	1194	1.7	1 (Ref)
	25–48	5	738	0.7	0.40 (0.15–1.07)
	49–72	11	449	2.4	1.46 (0.70–3.10)
	73–96	2	188	1.1	0.64 (0.15–2.72)
	97–120	6	126	4.8	2.84 (1.16–7.45)
Hong Kong 1993 [6]	0–24	4	217	1.8	1 (Ref)
	25–48	4	114	3.5	1.90 (0.48–7.89)
Nigeria 2010 [3]	0–24	6	1193	0.5	1 (Ref)
	25–48	2	876	0.2	0.45 (0.09–2.25)
	49–72	1	423	0.2	0.47 (0.06–3.91)
	73–96	1	198	0.5	1.00 (0.12–8.39)
	97–120	6	104	5.8	11.47 (3.83–38.26)
All trials	0–24	32	3054	1.0	1 (Ref)
	25–48	14	2065	0.7	0.68 (0.36–1.28)
	49–72	17	1059	1.6	1.74 (0.94–3.19)
	73–96	3	386	0.8	0.87 (0.26–2.89)
	97–120	12	230	5.2	5.81 (2.87–11.76)
	All	76	6794	1.1	

was 5.2 (95% CI 2.7% to 8.9%), below the 6% to 8% expected without treatment [8] but not significantly different from it.

Combining data from the two trials that included women until 120 h of delay in administration after an unprotected act of intercourse [2,3] did not change the results substantially. The ORs were, respectively, 0.41 (95% CI 0.18 to 0.95), 1.25 (95% CI 0.63 to 2.49), 0.72 (95% CI 0.22 to 2.39) and 4.83 (95% CI 2.39 to 9.73) for pregnancy in the second, third, fourth and fifth day with respect to the first day.

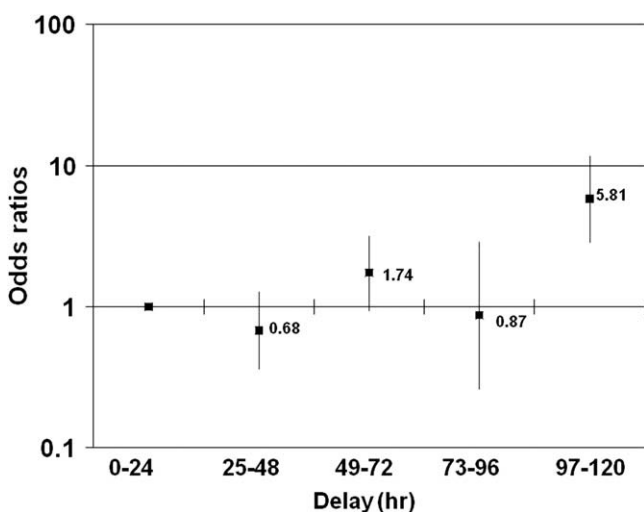


Fig. 1. Odds ratios of pregnancy for intervals of delay between an unprotected act of intercourse and administration of levonorgestrel after 24 h with respect to the first 24 h, with 95% CIs, for combined data of four WHO studies.

There was some indication of a different pattern in the effect of delay in two of the trials [1,6], where the pregnancy rates showed an increasing trend within 72 h. However, the heterogeneity of the effect of delay across trials was not significant at 5% ($p=0.0637$), $I^2=47.6\%$, indicating moderate heterogeneity.

4. Discussion

The number of women requesting EC after 72 h of an act of unprotected intercourse is usually small. By combining large trials using very similar protocols, the analysis presented in this article intended to accrue a sufficient number of women with this characteristic to reliably assess the effectiveness of levonorgestrel for EC in successive days within 120 h after an act of unprotected intercourse. Among 6794 women analyzed, 616 (9.1%) had treatment between 72 and 120 h after intercourse.

The results of the combined analysis show no evidence of an increase in pregnancy rates with the delay in administration of 1.5 mg of LNG, administered in a single dose or split into two doses 12 h apart, until the fourth day inclusive after an act of unprotected intercourse. Levonorgestrel is provided without prescription in many countries and is not associated with a delay in menses, unlike antiprogesterins such as mifepristone [9]. The mechanism of action of LNG has been studied and the drug is reported to have no effect on implantation, while mifepristone can prevent it [10,11]. In cultures where conservative religious views prevail and can influence health policies and public opinion, LNG is more accessible and acceptable to women than mifepristone or

other progestogen-receptor modulators. Similar levels of effectiveness of LNG through the fourth day (up to 96 h) are therefore an important finding.

However, an important increase in pregnancy rates, with a possible decrease in effectiveness of LNG, is apparent if administered after the fourth day of an act of unprotected intercourse. It is uncertain whether it still provides some degree of protection against unintended pregnancy if administered on the fifth day, albeit diminished from earlier administration. We hope this report will have addressed the concerns raised about the lack of data on the effectiveness of LNG when administered between 72 and 120 h of an unprotected act of intercourse [12].

The Cochrane review about interventions for EC [13] reports no difference in pregnancy rates between women with a delay within 72 h and those with a delay of 72 h or more, but the comparison reported by the authors includes LNG and mifepristone combined from one trial [2] and the delay of 72 h or more includes both the fourth and fifth day, which in our findings demonstrates a different efficacy. The results presented in this report, instead, are for LNG only and include a sufficient number of women to make separate comparisons of efficacy between the first and fourth day and between the first and fifth day.

It is worth noting that the comparison between the first and fifth day, although based on only 230 women, results in the 95% confidence interval for the OR not including 1, implying that receiving LNG on the fifth day was significantly less effective at the 5% level of significance than receiving it on the first day.

Two of the trials in this review [2,3] admitted women within 120 h of unprotected coitus. The aims of these trials was to compare different regimens, not to estimate absolute efficacy. Conclusions about whether LNG is effective — or not — compared to placebo or effective on particular days following unprotected intercourse should be made with caution, since a comparison to placebo was not included in those trials (it would not be ethical to do so) and the number of women with more than 72 h of delay was only 11–12% of the study participants.

This analysis has limitations: the comparison of pregnancy rates in the different categories of delay does not have the advantages of a randomized comparison and might be subject to bias due to different characteristics of women at trial entry in the different categories of delay. In particular, the expected pregnancies according to the day of the cycle on which unprotected intercourse occurred might have been different across the categories of delay. However, adjustment for baseline characteristics in the two oldest trials produced similar results (not presented), indicating that if bias was present, it was not a factor strongly affecting efficacy rates.

A second limitation is the difference between trials in the efficacy trend. Heterogeneity across trials in the effect of delay on pregnancy rates did not reach significance at the 5% level and the I^2 statistic indicated only ‘moderate heterogeneity’; therefore, we combined the results. However, two of

the trials included in this report [1,6] showed a linear increasing trend of pregnancy rates within 48 h [6] or within 72 h [1,4]. Given that the test for homogeneity might be underpowered, we do not exclude the possibility of a decrease in effectiveness in the second, third and fourth day with respect to the first day in certain settings or under particular conditions, possibly present in the settings of those two trials, and that we could not identify. A decrease in effectiveness of LNG with delay in administration would be consistent with its mechanism of action of preventing ovulation.

A third limitation is that the number of women receiving treatment between 72 and 120 h of an unprotected act of intercourse is only 616, from just two trials [2,3]. Although this number gave enough power to draw conclusions on the fifth day, more research would be desirable to confirm this finding, probably using surveillance epidemiological studies.

In conclusion, combining four studies with similar protocols, it was shown that there was no evidence of an increase in the risk of pregnancy when LNG 0.75 mg, repeated 12 h later or in a single dose of 1.5 mg, was administered for EC on the second, third and fourth day after unprotected intercourse, compared to administration on the first day. However, under certain conditions an increasing trend in pregnancy rates might exist within 72 h of administration; therefore it is advisable to administer LNG as soon as possible after unprotected intercourse. Delaying LNG administration until the fifth day after unprotected intercourse increases the risk of pregnancy over five times compared with administration within 24 h. It is uncertain whether LNG administration on the fifth day still offers some protection against unwanted pregnancy.

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