Timing of emergency contraception with levonorgestrel or the Yuzpe regimen

G Piaggio, H von Hertzen, D A Grimes, P F A Van Look, on behalf of the Task Force on Postovulatory Methods of Fertility Regulation

In the WHO Task Force study of levonorgestrel versus Yuzpe regimen of combined oral contraceptives for emergency contraception, we concluded that the efficacy of both treatments declined with increasing time since unprotected intercourse.[1] This conflicted with an earlier review of primarily observational studies which reported no significant effect of timing.[2] The WHO report suggested that "the discrepancy is due to lack of bias in randomised controlled trials compared with observational studies". An author of the review[2] has noted that randomisation itself could not account for the discrepancy.[3] We present further analyses of the WHO trial and offer several possible explanations for the discrepancies between these two reports.[1,2]

We included only participants with known outcomes. We excluded four women who were pregnant at enrolment (three assigned Yuzpe, one levonorgestrel). There was no information for another woman on coitus-to-treatment interval, accordingly 1950 women were included in this analysis (974 levonorgestrel 976 Yuzpe), among whom there were 38 pregnancies. Because the decreasing trend in efficacy with delay was found in each treatment group and the interaction of group by delay was not significant (p=0·44), we combined both groups in our analysis. We calculated the crude pregnancy rates for each 12 h interval of delay. Then we used logistic regression with group and a linear term for delay to estimate the odds ratio (95% CI) for delay, to test the linear trend and lack of fit of the model, and to adjust for possible confounders.

A consistent linear relationship existed between efficacy and the time from intercourse to treatment: pregnancy rates increased from 0·5% (two of 386) when treatment was given within 12 h of intercourse to 4·1% (six of 146) when given between 61 and 72 h after intercourse (figure). The odds ratio of pregnancy associated with treatment at a given time compared with treatment 12 h earlier was 1·46 (95% CI 1·20–1·77). The increasing trend in pregnancy rates with increasing delay was significant (p<0·01). The advantage with earlier treatment seemed to be maintained within the 72 h of delay studied, because the lack of fit of the model with the linear term for delay was non-significant (p=0·85 for the Hosmer and Lemeshow goodness-of-fit statistic). Differences in the rate of decline in efficacy between the two regimens, however, cannot be discarded because of the low power of the test for interaction.

As noted by Trussell,[3] the WHO trial randomised women to one of two treatment regimens and not to categories of delay, so that an assessment of the effect of delay on efficacy could be confounded by women's characteristics. Hence, we adjusted the estimate of the odds ratio successively for age, weight, body mass index, gravidity, cycle length, day of the cycle in which unprotected intercourse took place, and previous use of emergency contraception. This gave almost the same results.

Randomisation is not the only means to prevent bias in randomised controlled trials.[4] The rigorous methods of the WHO trial probably avoided some of the inherent biases in earlier case-series reports. These include the inability to account for women already pregnant at enrolment, large losses to follow-up, and unknown proportions of women with repeated acts of intercourse. The consistency between the WHO trial[1] and an earlier randomised controlled trial,[5] the statistically significant temporal effect seen with both regimens and biological plausibility suggest that the effect of timing of treatment is real.

With both the levonorgestrel and Yuzpe regimens, the earlier the treatment begins, the more effective it is. In the world's largest randomised controlled trial of these methods,[1] delaying the first dose by 12 hours increased the odds of pregnancy by almost 50%.

Delay (h)	0–12	13–24	25–36	37–48	49–60	61–72
No of women	386	522	326	379	191	146
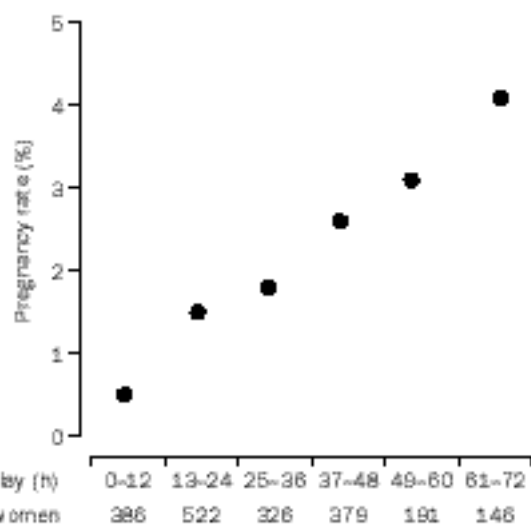
Effect of delay on pregnancy rates

1   Task Force on Postovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998; **352:** 428–33.
2   Trussell J, Ellertson C, Rodriguez G. The Yuzpe regimen of emergency contraception: how long after the morning after? *Obstet Gynecol* 1996; **88:** 150–54.
3   Trussell J. Emergency contraception: WHO Task Force study. *Lancet* 1998; **352:** 1222–23.
4   Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; **276:** 637–39.
5   Ho PC, Kwan MSW. A prospective randomized comparison of levonorgestrel with the Yuzpe regimen in post-coital contraception. *Hum Reprod* 1993; **8:** 389–92.