Mifepristone and levonorgestrel are effective and well-tolerated when used for emergency contraception. Mifepristone mid-dose should be the method of choice for emergency contraception, although it is not available in several countries. To ensure compliance, a single-dose regimen of levonorgestrel is preferable over repeated doses.

RHL Commentary by Mittal S and Aggarwal P

1. Introduction

Even though a wide variety of contraceptive choices are available in India, contraceptive prevalence in the country is only 56% as per the WHO Global Health Statistics 2012. This figure also holds true for the entire WHO South-East Asia region (1). Stratified by income, contraceptive prevalence in the low-income group within the region is only 35%, while it increases to 52% and 80% in the lower-, middle- and upper-middle-income groups (1). Most couples in India do not want to use a contraceptive method on a long-term basis for the fear of side-effects, especially the oral pill and intrauterine devices (IUDs), or do not like to use a method linked with coitus (barrier methods). Hence, unwanted and unplanned pregnancies are common.

As per data from WHO, 21.6 million unsafe abortions occurred globally in 2008, out of which 47 000 women died from abortion-related complications, contributing to 13% of global maternal mortality (2). An estimated 80 million unintended pregnancies will occur in 2012 in the developing world, resulting in 30 million unplanned births, 40 million abortions and 10 million miscarriages (3). A considerable proportion of these abortions can be prevented by the timely use of emergency contraception.

Emergency contraception (EC) involves using a drug or copper IUD to prevent pregnancy shortly after unprotected intercourse. There are several emergency contraceptives in use today. However, their side-effects, convenience of use, and safety and efficacy profiles vary. It is imperative for the health-care provider to be aware of these variations so as to counsel and serve women appropriately. The objective of this Cochrane review (4) was to determine which EC method following unprotected intercourse is the most effective, safe and convenient to prevent pregnancy.

2. Methods of the review
The review examined randomized controlled and controlled clinical trials comparing different methods of emergency contraception or any method with expectant management, reporting on clinical outcomes, namely efficacy (number of pregnancies), side-effects, ectopic pregnancy and delay in menses. Studies involving women with regular menses attending for EC services following a single act of unprotected intercourse were eligible. Studies comparing emergency contraceptives provided in advance, emergency contraceptives available over the counter, or once-a-month methods were not included.

The trials were identified and retrieved: (i) by electronic searches of the Central/Cochrane Controlled Trials Register, PubMed, EMBASE, Popline, CINAHL, LILACS and Chinese biomedical databases; (ii) from WHO resources; (iii) Emergency Contraception World Wide Web; and (iv) pharmaceutical companies and content experts until July 2011. All trials were checked for relevance, randomization, quality and allocation concealment (5) by two review authors independently. Data extraction was done in duplicate including the following variables: intervention/control treatment, clinical outcomes, methodology and demographics. Altogether, 81 studies were excluded for different reasons. The treatment results were calculated using relative risk (RR) estimates with the 95% confidence interval (CI). In the presence of statistically significant heterogeneity a random-effects model was applied. The outcomes for missing patients were imputed under two extreme scenarios (i.e. all missing in one arm had an event and all missing in the other arm did not have an event and vice versa). Besides comparison of different regimens, other factors affecting the success of emergency contraception (coitus-treatment interval and risk status of women) were also evaluated. Since the last version of this review, 19 new studies have been added and ulipristal acetate (UPA) has been approved by the US Food and Drug Administration for use as EC. The review is unbiased and thorough. The data are clearly tabulated and graphically depicted for different methods taking in consideration all the parameters evaluated.

3. Results of the review

One hundred trials (86 of them conducted in China) with 55,666 women were included in the review. These trials compared different methods of emergency contraception with each other and expectant management. The methods included high-dose estrogen, Yuzpe regimen (estrogen plus progestogen), levonorgestrel (LNG) (single-dose and split-dose), danazol, mifepristone (varying doses), anordrin, mifepristone with anordrin, misoprostol, tamoxifen, gestrinone, UPA and the copper IUD CuT200.

Comparative evaluation of different interventions found that any form of emergency contraception was better than no intervention. LNG was more effective than the Yuzpe regimen (RR 0.54) with fewer side-effects. A single dose (1.5 mg) of LNG was as effective as the split-dose regimen (two doses 0.75 mg each), but with higher frequency of headache and heavy menses. LNG split-dose was compared in two regimens (24h vs. 12h) and showed similar efficacy in both regimens, but with a greater risk of pregnancy in the high-risk group with 12h dosing. LNG within 72h of intercourse was more effective than after 72h (RR 0.51, 95% CI 0.31–0.84).

Mid-dose (25–50 mg) mifepristone was more effective in preventing pregnancy compared with LNG (RR 0.64, 95% CI 0.45–0.92) with fewer side-effects, but with delay in menses. Low-dose (<25mg) mifepristone was also more effective than LNG (RR 0.7, 95% CI 0.50–0.97), but this did not hold true when only high-quality studies were included. No trials compared high dose (>50mg) mifepristone with LNG. In studies comparing high (>50mg), mid and low doses of mifepristone with each other, all were equally efficacious but the risks of bleeding and menstrual delay increased in a dose-related manner. Coitus-treatment time interval did not affect the efficacy of mifepristone.

Mifepristone was more effective than Yuzpe regimen (RR 0.14, 95% CI 0.05–0.41), danazol (RR 0.10) and anordin (RR 0.26, 95% CI 0.11–0.63) and had fewer side-effects of nausea, vomiting, headache, dizziness, tiredness and abdominal pain. The Yuzpe regimen did not have any significant effect on the menstrual cycle, but the other three were associated with menstrual delay. Combining mifepristone with anordrin, tamoxifen,
misoprostol, or methotrexate did not have any significant effect on the pregnancy rate, but side-effects and delay in return of menses were more common when mifepristone was combined with anordrin. Mifepristone and gestrinone were equally effective.

UPA was more effective in 5-day data after unprotected intercourse as compared to LNG in 72h (RR 0.59, 95% CI 0.35–0.99), but not when both were compared in 3-day data. UPA also delayed the return of menses. Coitus-treatment time interval did not affect the efficacy of UPA.

Administration of a single-dose of the Yuzpe regimen (half the normal dose given once) did not decrease its efficacy, but its side-effect profile improved significantly. Administration of the Yuzpe regimen within 24h of intercourse was more effective than after 24h (RR 0.47, 95% CI 0.26–0.88).

The use of the copper IUD for emergency contraception was most effective and provided ongoing contraception. IUD efficacy for emergency contraception was higher the sooner after intercourse the IUD was used. Overall, pooled data showed that the risk of pregnancy was higher in the high-risk group (women who had further acts of intercourse during the same cycle in which EC was used) as compared with the low-risk group (those who did not have further acts). Five cases of ectopic pregnancy were reported, three following mifepristone use and two after split-dose LNG. Eleven healthy infants were reportedly delivered with no adverse effects following the use of LNG, Yuzpe regimen, danazol and mifepristone.

4. Discussion

4.1 Applicability of the results

Although most of the studies included in the review are from China, there are several multi-centre trials as well, and thus the findings of this review are applicable to all settings. The review suggests that mifepristone and LNG are effective and well-tolerated when used for emergency contraception. Mifepristone mid-dose should be the method of choice for emergency contraception; however, it is not available in several countries. To ensure compliance, a single-dose regimen of LNG is preferable over repeated doses. Currently, LNG is being marketed in several developing countries as a dedicated method of EC because of its easy availability and lower cost compared with mifepristone. Delay in the onset of menses is a drawback with the use of mifepristone and UPA for emergency contraception, as the woman may continue to be anxious until her menses restart. UPA was more effective than LNG and can be an alternative where this drug is accessible and affordable, but more studies are needed. UPA is available on prescription in Europe but it is not available in many low-resource settings including India. The Yuzpe regimen should be used only when the above options are not available due to higher incidence of side-effects and lower efficacy. A copper-bearing IUD can be offered to a woman requesting long-term contraception. Women should be advised to use an emergency contraception method as early as possible after unprotected intercourse and to abstain from further intercourse or to use alternative methods of contraception. Other methods like anordrin, tamoxifen, danazol and misoprostol have been used mainly for research purposes and offer no advantage.

Past history of ectopic pregnancy was previously considered a contraindication for the use of EC, but with the present review reporting only five ectopic pregnancies in 55,666 women, EC can be considered to be safe.

4.2 Implementation of the intervention

The full potential of emergency contraception can be realized only when women are made aware of the existence of these methods and the need to use them within the short time frame of their efficacy. Such awareness is still limited in many developing countries. In India, a survey of 4000 women aged 18–55 years in the state of Delhi revealed very low (3.2%) awareness about emergency contraception (6). Awareness in rural areas was less than 2%. Evaluation of knowledge and views of doctors about emergency contraception revealed poor knowledge among general practitioners (7). Even specialist physicians were not aware about
the appropriate dosages, timing of use, and mechanism of action or availability of emergency contraceptives. Thus, the most important step is to increase awareness of emergency contraception in under-resourced settings.

Information about the availability of these methods needs to be provided to both health-care providers and potential users. In 2001, a consortium was organized for national consensus on emergency contraception in India (8). It addressed several issues including, choice of the drug, distribution protocol, client information and counseling and training of health-care providers. Guidelines were formulated and LNG was introduced in the country as a two-pill pack, each containing 0.75 mg of the drug, to be taken 12 hours apart, within 72 hours of unprotected intercourse. In view of the new research findings reported in this Cochrane review, the guidelines for emergency contraception will need to be revised. Single dose (1.5 mg) LNG EC pill is already being marketed in India.

A countrywide public awareness campaign would be needed to inform people about the advantages of this intervention. The Consortium for Emergency Contraception in India met again in 2005 for expanding the access of EC (9). Since then, over-the-counter availability of the two-pill / single pill levonorgestrel pack has facilitated wider utilization of the method in India, especially in under-resourced settings where availability of doctors for prescribing the method is limited. However, repeated use and misuse of the method emerged as a new concern and Consortium met again in 2009 and came out with recommendations for rational use of EC. With over-the-counter availability of these methods, an opportunity for providing counseling for regular contraception is missed; however, the Government of India is now empowering even field workers (ASHA – Accredited Social Health Activist) to carry the EC pill as well as condoms and oral contraceptive pills to the women at their doorstep.

4.3 Implications for research

To help with policy formulation, there is a need to conduct large-scale field trials to determine efficacy and feasibility of the use of emergency contraception at the peripheral level in developing countries. Research is also needed to evaluate LNG and mifepristone in comparison with IUDs and to evaluate the cost-effectiveness of different efficacious regimens. The efficacy of LNG, UPA and mifepristone in relation to time since unprotected intercourse is not confirmed and more studies are needed. The efficacy of UPA as compared to mifepristone also needs more research to guide appropriate counselling.

References

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