Progestogens in combined oral contraceptives for contraception

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Pills with first-generation progestogens are more likely to produce unacceptable side-effects compared with those containing the second- and third-generation progestogens. The second- and third-generation pills are similar in terms of effectiveness and of side-effects, except for the much lower cost of the former.

RHL Commentary by Festin M

1. EVIDENCE SUMMARY

Combined oral contraceptives (COCs) have an estrogen and a progestogen component. Existing progestogen compounds can be classified as first-, second- and third-generation.

First-generation progestogens include, among others, norethisterone (NET), norethindrone (NE), ethynodiol diacetate, and lynestrenol (LYN). Levonorgestrel (LNG) and norgestrel (NG) are the second-generation progestogens, and third-generation progestogens include desogestrel (DSG), gestodene (GSD) and norgestimate (NGM). Second-generation progestogens were introduced into the market in the 1970s and third-generation progestogens were introduced a decade later. Currently, LNG is probably the most widely used progestogen and is predominantly combined with 30 µg ethinyl estradiol in combined oral contraceptive pills.

The review compares currently available low-dose COCs (containing different progestogens) in terms of their effectiveness, safety and acceptability (protection against pregnancy, cycle control, side-effects and use continuation rates). Twenty-two trials (including 18 sponsored by the pharmaceutical industry) are included. Among these, in only five trials there was an attempt at blinding.
Method discontinuation was lower with second- compared with first-generation progestogens (relative risk [RR]: 0.79; 95% confidence interval [CI]: 0.69–0.91). Cycle control appeared to be better with second- compared with first-generation progestogens for both mono- (RR: 0.69; 95% CI: 0.52-0.91) and triphasic (RR: 0.61; 95% CI: 0.43–0.85) preparations. GSD (3rd gen.) and LNG (2nd gen.) yielded similar rates for contraceptive effectiveness, spotting, breakthrough bleeding and the absence of withdrawal bleeding. However, there was less intermenstrual bleeding in the GSD group (RR: 0.71, 95% CI: 0.55–0.91). All acceptability indices showed that third- and second-generation (LNG) progestogens were preferred over those containing first-generation progestogens. More pregnancies occurred when pills containing 20 µg ethinyl estradiol (EE) were used. Compared with pills containing DSG, those with GSD yielded better cycle control, although the continuation rate was higher in women using DSG-containing pills. The results of trials of pills containing drospirenone (DRSP) were similar to those with DSG with regard to pregnancy prevention, cycle control and side-effects.

2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

Many of the countries that are labelled as under-resourced are also those with high population growth rates or with large populations. Factors considered by family planning programmes in such countries include effectiveness of the method, safety and absence of adverse effects, and cost.

Many contraceptive techniques are currently used in the Philippines, but the contraceptive prevalence rate has only reached 49% and has been levelling off in recent years. Modern methods account for only 33.4% (1). In 2003, the total fertility rate was 3.5 children per woman, with an unplanned fertility rate of 1.0; the rate for unmet need for family planning was 17.3%. The most popular method is the oral contraceptive pill (13%). Based on education and social economic status, those in the lowest quartiles have a lower rate of use compared with those in the other quartiles (1). The reported reasons for not using steroid hormone contraceptives include health concerns (14.3%) and the fear of side-effects (14.2%) (1). The latter may include disturbances in normal menstrual patterns.

2.2. Applicability of the results

Some of the drugs listed in the review are relatively new. These may not have been thoroughly evaluated for effectiveness and for safety and yet may be available in under-resourced countries for drug evaluation or for the promotion of rational drug use. Thus, a proper evaluation of these products may have to be done in these settings in order to come up with appropriate recommendations for their use.

A review of the drug catalogue in the Philippines shows that preparations with second-generation progestogens (LNG and NG) and third-generation progestogens (DSG and GSD) are on sale in the country (2). Lynestrenol which is classified as a first-generation progestogen is being marketed as a progestogen-only contraceptive compatible with breastfeeding. NET is available but is more commonly used for the management of menstrual bleeding disorders rather than for contraception. Cyproterone is also marketed in a combined contraceptive pack as a contraceptive with favourable dermatological benefits. The second-generation progestogens are very common and are inexpensive, with LNG-containing cycle pack of pills costing less than a dollar. Pills containing third-generation progestogens cost many times more. The side-effects of the second- and third-generation progestogens are generally similar (LNG versus GSD) except for inter-menstrual bleeding. Women should be given this information so that they may be able to anticipate the effects, even though they are relatively minor. Pills with first-generation progestogens are not very common in the market anymore (in the Philippines).

2.3. Implementation of the intervention
Pills with first-generation progestogens are more likely to produce unacceptable side-effects compared with those containing the second- and third-generation progestogens, as noted in the review. The other main concern is cost. The second- and third-generation pills were found to be similar in terms of effectiveness and of side-effects, except for the much lower cost of the former. These trade-offs have to be considered in advising women about oral pills. The differences between the different types of pills in side-effects should be prepared as an information package for health-care providers to allow them to easily transmit this information to their clients. Cost and accessibility becomes the bottom line for users when drugs are similar in terms of effectiveness and side-effects.

3. RESEARCH

The oral contraceptive pill and its components have been well researched. However, future research could focus on conducting large, independent (of the pharmaceutical industry), well-designed randomized trials that compare third- and second-generation progestogens, in terms of well-defined and standardized outcomes. There may also be the need to explore other indicators of acceptability such as libido, sexual performance, and satisfaction scores. Studies may also need to look into the blinding of the assessment of user failure or method failure to reduce bias. It may also be useful to study how best health-care workers can transmit information about oral contraceptives to users and potential users to improve their knowledge about the method and reduce fear of side-effects, thereby increasing continuation rates.

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References


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