Recent advances in hormonal contraception

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Abstract

This report reviews some of the new studies regarding new hormonal contraceptive formulations (e.g., Yaz, Qlaira®, extended-cycle or continuous combined contraceptives, subcutaneous depot medroxyprogesterone acetate, and ulipristal acetate as an emergency contraceptive). Recent data on the relationship between hormonal contraceptive use and bone health are also reviewed.

Introduction and context

Hormonal contraception is one of the most widely used contraceptive modalities and provides very good efficacy and low failure rates. Continued research has explored and introduced new formulations and clarified some of the concerns regarding the use of hormonal contraceptives, and indeed overall reductions in all-cause and heart disease mortality rates were recently reported by the UK Royal College of General Practitioners study [1]. This paper reviews some of the important studies on hormonal contraception reported recently.

Recent advances

Combined hormonal contraceptives

Drospirenone (DRSP) represents the newest generation of progestogen used in oral contraceptive pills. A large multicenter prospective observational study [2] assessed a combined oral contraceptive (COC) containing 30 μg ethinylestradiol (EE) and 3 mg DRSP (Yasmin®; Bayer AG, Leverkusen, Germany), which improved water retention symptoms and bleeding pattern. However, the study is limited by its non-comparative design. Further comparative studies versus the older COCs are warranted to provide stronger evidence.

An ultra-low-dose preparation containing 20 μg EE and 3 mg DRSP in a novel 24/4 regimen (Yaz; Bayer AG) has been marketed recently. Its efficacy is similar to, if not better than, that of older COCs and has an acceptable bleeding pattern. Yaz is currently the only COC with reported evidence for and approved indication in the treatment of emotional and physical symptoms of premenstrual dysphoric disorder and has shown improvement in productivity, social activities, and relationships [3-5].

Another new preparation (Qlaira®; Bayer AG) containing 17-beta-oestradiol instead of EE as the oestrogen component has been marketed recently. It contains oestradiol valerate (E2V) and dienogest in a multiphasic regime that is optimised to provide good efficacy (adjusted Pearl index of 0.34) and at the same time satisfactory cycle control [6,7]. It is the first preparation using natural oestradiol, but clinical benefits over the older preparations remain to be explored in comparative studies.

Progestogen-only contraceptives

Depo-subQ provera 104 (Pfizer Inc., NY, USA), a subcutaneous preparation of depot medroxyprogesterone acetate (DMPA) 104 mg in 0.65 mL, has been introduced in recent years. The slightly lower dosage, optimized for delivery by subcutaneous administration, was determined in pharmacokinetic studies on both Caucasian and Asian women to meet the minimum serum concentration required to provide consistent
Hormonal contraceptives and bone health

Emergency contraception

The levonorgestrel (LNG)-only regimen is now a standard for emergency contraception (EC). The effectiveness of the single-dose regimen (LNG 1.5 mg) is similar to that of split-dose LNG and could minimize compliance problems and is currently the recommended regime approved for use up to 72 hours following unprotected sexual intercourse [10].

Progesterone receptor antagonists/modulators can also be used for EC. Mifepristone is superior to LNG in efficacy [10] but is available only in China for EC. Doses of 25-50 mg are very effective, and lower doses (less than 25 mg) may be equally good. Menstrual delay is common with mifepristone. The progesterone receptor modulator, ulipristal acetate (CDB-2914), is a new option. Ulipristal acetate 30 mg (ellaOne; HRA Pharma, Paris, France) has been recently marketed in Europe as an EC. A meta-analysis of two randomised controlled trials suggested that it is more effective than LNG (failure rate 1.4% versus 2.2%), and it can be used up to 5 days after unprotected sexual intercourse [11].

Hormonal contraceptives and bone health

Multiple reports in the literature have suggested an association between DMPA use and a decreased bone mineral density (BMD), which is at least partially reversible upon discontinuation [12,13], but the clinical significance has remained unclear, particularly with regard to the long-term risk of clinical fracture. Recently, a population-wide case control analysis of contraceptive use in Danish women who had clinical fractures was reported; this demonstrated a statistically significant increase in fracture risk (adjusted odds ratio 1.44, 95% confidence interval 1.01-2.06) in DMPA-users versus non-users, with the risk most pronounced in women more than 50 years old or those who used it for more than 4 years [14]. However, there were only a small number of DMPA-users in the cohort, and due to the nature of the study design, not all potential confounders might have been addressed. A large-scale randomised controlled trial sufficiently powered to detect a difference in fracture risk would be extremely difficult practically.

Further studies in other populations would be warranted to gather further data. Another multicenter prospective randomised controlled trial compared subcutaneous DMPA with the conventional intramuscular DMPA over a 2-year period and found them to be very similar in regard to a small reversible BMD loss [15].

On the other hand, it is increasingly recognised that combined hormonal contraceptives might also have a potential impact on bone mass accrual in adolescents and young adults. A systematic review found inconsistent data relating to effects of COCs on bone mass in adolescents and young women, and only one good quality study was identified; it concluded that COC-users did not gain as much bone mass as non-users [16]. A 4-year non-randomised follow-up study found a significantly lower increment in the mean adjusted bone mineral content in young adolescent (12-19 years old) users of combined hormonal contraceptive for more than 2 years [17]. A population-wide case control analysis of COC use in Danish women who had clinical fractures suggested that there is no clear increase in fracture risk with COCs [18].

Implications for clinical practice

The DRSP-containing combined hormonal contraceptives offer similar contraceptive efficacy with specific benefits of improved water retention symptoms and, for Yaz, a licensed use for treatment of premenstrual dysphoric disorder. A new COC preparation that contains the natural 17-beta-oestradiol and that is similar to the conventional COCs in efficacy and acceptable cycle control has been marketed; however, its benefits over the older COCs are yet to be explored and it is markedly more expensive. A subcutaneous form of DMPA provides efficacy and side effect profiles that are similar to, if not more favorable than, those of the conventional intramuscular DMPA and provides a self-injectable option. In regard to EC, the single-dose LNG-only regime is a recommended first-line option. A new product containing ulipristal acetate provides a more effective alternative to LNG and can be used up to 5 days after unprotected sexual intercourse. Most reports in the current literature found a negative effect of both DMPA and combined hormonal contraceptives on BMD, but the clinical significance remains debatable. The evidence so far is not adequate to suggest any limit on their use or any additional monitoring in users who are otherwise healthy.

Abbreviations

BMD, bone mineral density; COC, combined oral contraceptive; DMPA, depot medroxyprogesterone acetate; DMPA-IM, intramuscular preparation of depot medroxyprogesterone acetate; DRSP, drospirenone;
EC, emergency contraception; EE, ethinylestradiol; LNG, levonorgestrel.

Competing interests
The authors declare that they have no competing interests.

References
1. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ: Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010, 340:C927.

2. Endrikat JS, Milchev NP, Kapamadzija A, Georgievska J, Gerlinger C, Schmidt W, Froze S: Bleeding pattern, tolerance and patient satisfaction with a drospirenone-containing oral contraceptive evaluated in 3488 women in Europe, the Middle East and Canada. Contraception 2009, 79:428-32.

3. Fenton C, Wellington K, Moen MD, Robinson DM: Drospirenone/Ethinylestradiol 3 mg/20[micro]g (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. Drugs 2007, 67:1749-65.

4. Lopez LM, Kaptein AA, Helmerhorst FM: Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database Syst Rev 2009, 2:CD006586.

5. Anttila L, Kurz M, Marr J: Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive. Contraception 2009, 80:445-51.

6. Fruzzetti F, Bitzer J: Review of clinical experience with estradiol in combined oral contraceptives. Contraception 2010, 81:8-15.

7. Nahum GG, Parke S, Wildt L, Palacios S, Roemer T, Bitzer J: Efficacy and tolerability of a new oral contraceptive containing estradiol and dienogest. Obstet Gynecol 2008, 111(4 Suppl):15S.

8. Jain J, Jakimiuk AJ, Bode FR, Ross D, Kaunitz AM: Contraceptive efficacy and safety of DMPA-SC. Contraception 2004, 70:269-75.

9. Westhoff C, Jain JK, Milsom I, Ray A: Changes in weight with depot medroxyprogesterone acetate subcutaneous injection 104 mg/0.65 ml. Contraception 2007, 75:261-7.

10. Cheng L, Gulmezoglu AM, Piaggio G, Escurra E, Van Look PF: Interventions for emergency contraception. Cochrane Database Syst Rev 2008, 2:CD001324.

11. Glasier AF, Cameron ST, Fine PM, Logan SJS, Casale W, van Horn J, Sogor L, Blithe DL, Scherrter B, Mathe H, Jaspart A, Ulmann A, Gainer E: Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010, 375:555-62.

12. Curtis KM, Martins SL: Progestogen-only contraception and bone mineral density: a systematic review. Contraception 2006, 73:470-87.

13. Guilbert ER, Brown JP, Kaunitz AM, Wagner MS, Berube J, Charbonneau L, Francoeur D, Gilbert A, Gilbert F, Roy G, Senikas V, Jacob R, Morin R: The use of depot-medroxyprogesterone acetate in contraception and its potential impact on skeletal health. Contraception 2009, 79:167-77.

14. Vestergaard P, Rejnmark L, Mosekilde L: The effects of depot medroxyprogesterone acetate and intrauterine device use on fracture risk in Danish women. Contraception 2008, 78:459-64.

15. Kaunitz AM, Darney PD, Ross D, Wolter KD, Speroff L: Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception 2009, 80:7-17.

16. Martins SL, Curtis KM, Glasier AF: Combined hormonal contraception and bone health: a systematic review. Contraception 2006, 73:445-69.

17. Pikkarainen E, Lehtonen-Veromaa M, Mottonen T, Kautiainen H, Viikari J: Estrogen-progestin contraceptive use during adolescence prevents bone mass acquisition: a 4-year follow-up study. Contraception 2008, 78:226-31.

18. Vestergaard P, Rejnmark L, Mosekilde L: Fracture risk in very young women using combined oral contraceptives. Contraception 2008, 78:358-64.