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Review article

Current issues and available options in combined hormonal contraception

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Abstract

Development of hormonal contraception marked a revolutionary step in social change that has improved the lives of women and families worldwide. Since the first oral contraceptive was introduced in the 1960s, hormonal contraception has undergone various stages of advancement. Today, oral contraceptive regimens are safer and more tolerable, with equal or improved efficacy, than the early formulations. Incremental decreases in the dose of estrogens have helped to alleviate some of the unwanted estrogenic side effects of combined hormonal contraceptives. Progestogens have also evolved over time, and newer generations of progestins have minimal side effects. New delivery methods have further extended the range of options available to women. Among these, the transdermal patch and vaginal ring are widely used. This review examines available combined hormonal contraceptive options and compares them, where data are available, for efficacy, safety, cycle control, adverse events profiles and associated risks, and user preference and satisfaction. We also examine particular areas of interest, including bone mineral density, venous thrombosis and use of antiepileptic drugs.

Keywords: Hormonal contraceptives; Vaginal ring; Oral contraception; Transdermal patch

1. Introduction

Since the introduction of the first combined hormonal contraceptive in 1960, there have been many developments toward the goal of minimizing side effects and improving compliance without compromising efficacy [1]. The first of these advancements was a decrease in hormone concentrations to the currently used low-dose formulations [2]. Oral contraceptives (OCs) combining a progestin with ≤35 mcg ethinyl-estradiol (EE) are now standard, with the exception of select circumstances such as in women using antiepileptic drugs (AEDs) [3]. Formulations with EE 20 mcg have further been shown to decrease estrogenic effects such as bloating and breast tenderness without compromising efficacy [4,5]. A recent analysis of the continuing Royal College of General Practitioners (RCGP) Oral Contraception Study [6] demonstrated that, among approximately 46,000 women followed since 1968, users of OCs had significantly lower rates of death from any cause and significantly lower rates of death from cancer, cardiovascular disease and other diseases than those who had never used OCs.

Subsequent development of newer-generation progestins resulted in stronger progestogenic activity and decreased androgenic effects such as acne, hirsutism and lipid changes, as well as other unwanted estrogenic effects such as nausea and fluid retention [7]. The latest development in combined OCs (COCs) has been in incorporating more physiological forms of estrogen with a progestin [8–10]. Nonoral delivery methods represent another recent advancement in combined hormonal contraception, including the contraceptive vaginal ring, the transdermal contraceptive patch and monthly injections of estrogen plus progestogens. In addition to the elimination of the need for daily compliance, these alternative delivery methods have different pharmacokinetic profiles that may further optimize plasma hormone levels. Additionally, shortening or eliminating the pill-free interval may potentially improve contraceptive efficacy and reduce side effects [11–13].

Despite these advances, issues remain associated with the use of combined hormonal contraceptives. The purpose of this review is to describe these issues in the context of the various methods of combined hormonal contraception

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and how they compare in order to assist health care providers make optimal contraceptive recommendations to their patients.

2. Pharmacokinetic profiles

While progestins alone can provide contraceptive efficacy, the estrogen component of combined contraceptives improves cycle control, but at the expense of potential estrogen-related side effects such as nausea, breast tenderness and thrombophlebitic or thromboembolic risk [2,14]. Therefore, one of the goals of combined hormonal contraception is to provide the lowest estrogen exposure while maintaining good cycle control. Simply reducing the dose of EE, however, does not guarantee that estrogenic exposure will be reduced, as pharmacokinetic parameters can vary, particularly according to route of administration [15–19]. Oral EE is subject to an extensive first-pass effect and enterohepatic recirculation [18] and has a bioavailability of 38%–48% [17]. It is extensively bound to serum albumin, and only 1% circulates as free EE [17]. Ethinyl-estradiol is metabolized primarily by 2-hydroxylation catalyzed by cytochrome P-450 3A4 before conjugation to an inactive glucuronide and excreted primarily in the urine [17,18].

Nonoral (vaginal, transdermal) administration of EE avoids first-pass metabolism and may have less effect on hepatic function; however, vaginal and oral treatment had a similar effect on biomarkers of hepatic function [20,21], whereas transdermal administration had much less effect than oral administration [22,23]. In a study of 41 women with hysterectomy, oral 17β-estradiol (E2) was compared with transdermal E2 in a crossover study over two consecutive 12-week treatment periods with a 1-week washout period between treatment periods [24]. Oral E2 increased triglycerides and high-density lipoprotein cholesterol and decreased total and low-density lipoprotein cholesterol. Transdermal E2 did not alter lipid profiles. It is therefore necessary to examine pharmacokinetic and pharmacodynamic profiles of combined products following administration.

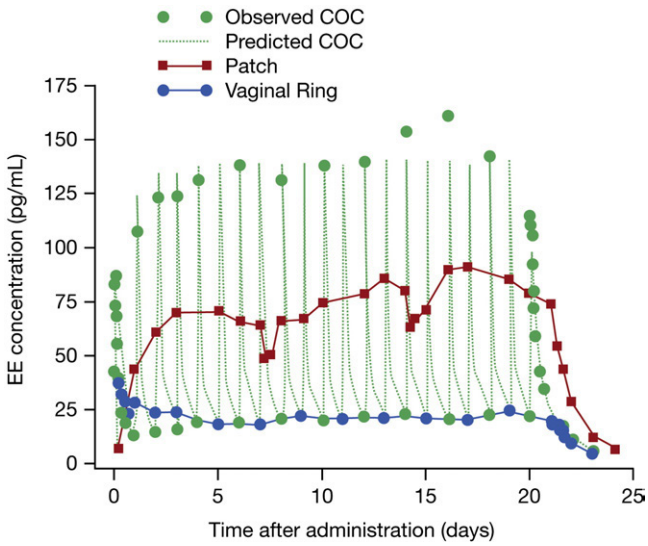

Fig. 1. Mean (concentration vs. time curve) levels of EE in an oral contraceptive, the contraceptive vaginal ring and the contraceptive transdermal patch. The vaginal ring releases 15 mcg EE and 120 mcg etonogestrel per day. The transdermal patch releases 20 mcg EE and 150 mcg NGMN per day. The COC used releases 30 mcg EE and 150 mcg LNG per day. Modified from van den Heuvel et al. [19], with permission from Elsevier.

Table 1
Pharmacokinetics of the EE component of combined hormonal contraceptives using different delivery methods

Pharmacokinetic parameter	Vaginal ring	Patch	COC
C_{max}±SD, pg/mL	37.1±5.1	105±2.4	168±29.5
t_{max} (range), h	6.0 (6.0–11.8)	372 (240–456)	386 (337–434)
AUC_{0-21}±SD, ng·h/mL	10.6±2.5	35.8±5.5	21.9±2.9

The vaginal ring releases 15 mcg EE and 120 mcg etonogestrel per day. The transdermal patch releases 20 mcg EE and 150 mcg NGMN per day. The COC used releases 30 mcg EE and 150 mcg LNG per day. AUC_{0-21}, area under the curve (0–21 h); C_{max}, maximum serum EE concentrations; SD, standard deviation; t_{max}, time of peak serum EE concentration. Modified from van den Heuvel et al. [19].

Patterns of serum concentrations of EE over time vary considerably depending on the delivery system (Fig. 1) [19]. Daily intake of OCs creates peaks and troughs in EE concentrations, whereas the ring and patch deliver more constant levels of EE [19]. Assessment of individual pharmacokinetic parameters (Table 1) shows that EE exposure is lowest with the vaginal ring and that a higher exposure is observed with a COC containing levonorgestrel (LNG) 150 mcg plus EE 30 mcg. The patch was associated with the greatest EE exposure ($p<.05$ for both ring and pill) [19]. The patch AUC was three times greater than the ring AUC, yet the daily dose released by the patch (20 mcg EE) was not three times higher than the ring (15 mcg EE), and both delivery systems avoid first-pass metabolism. Of note, the t_{max} was more variable with the patch than for either method.

It has been suggested that the type of progestin used in COCs influences the metabolism of EE, increasing or decreasing bioavailability and therefore altering estrogenic exposure. One study in particular reported 70% higher serum EE levels when combined with gestodene (GES) compared with desogestrel (DSG) even though the administered EE dose (30 mcg) was the same in both formulations [25]. However, attempts to reproduce these initial findings, using similar as well as different analytical methods and greater numbers of subjects, were unsuccessful [26–31], indicating that GES and DSG did not alter EE concentrations.

3. Efficacy

Contraceptive efficacy is often calculated in clinical trials using the Pearl Index (PI), which is used as an estimation of