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OC Practice Guidelines: Minimizing Side Effects

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ABSTRACT: The side effects of oral contraceptives (OCs) can be minimized by appropriate OC selection. Side effects or perceived side effects that manifest themselves physically—e.g., weight gain, breakthrough bleeding (BTB), nausea, headache, breast tenderness, mood swings, acne, and hirsutism—are the most common causes of premature discontinuation of oral contraception. The relative androgenicity of the progestin component of combination OCs has become an important differential in selecting OC formulations. Several studies have indicated that preparations with less androgenic potential can minimize some of the "physical" side effects and adverse metabolic effects traditionally associated with oral contraception. Acne and hirsutism, common pre-existing conditions that are clearly related to the androgenicity of the progestin component, can be eliminated or improved by use of OCs with low androgenic activity. Many women perceive that OCs cause weight gain; although weight gain is to some extent androgen related, most studies comparing low-androgenic OCs with medium- or high-androgenic preparations have found little or no change in weight regardless of formulation. BTB, which usually subsides within a few months, is related to the dose, potency, and ratio of the estrogen and progestin in the OC formulation. Low-estrogen-dose OCs (≤35 µg ethinyl estradiol [EE]) containing less androgenic progestins are associated with bleeding patterns as acceptable as older low-estrogen-dose formulations. The same analysis found that smoking cigarettes promotes BTB in women who use OCs. There is no convincing evidence that the use of one progestin or another is less likely to cause or exacerbate headache; however, changing preparations sometimes reduces the incidence. Women with persistent headaches during the pill-free interval may benefit from a longer cycle of OC treatment. Nausea and breast tenderness are primarily estrogen-related effects; if a woman experiences persistent nausea, switching to an OC formulation containing 20 µg EE may be appropriate as long as the patient is cautioned that BTB is more likely. Mood changes are a common, highly subjective complaint whose relationship to OC use is hard to assess. Concerns about the potentially deleterious effects of combination OCs on lipid/lipoprotein and carbohydrate metabolism have been substantially diminished by new epidemiologic findings relative to cardiovascular disease as well as by the development of low-androgenic progestins. Formulations containing these progestins lower LDL cholesterol and increase HDL cholesterol; they do not affect carbohydrate metabolism as much as older, more androgenic formulations. *Int J Fertil* 42(Suppl 1):158–169, 1997

KEY WORDS: oral contraceptives, side effects, androgenicity, estrogen, progestin

INTRODUCTION

A WIDE VARIETY OF EFFECTIVE AND safe oral contraceptive (OC) formulations is currently available. As a general rule, a combination OC with the lowest dose of progestin and estrogen that will maintain contraceptive protection, minimize side effects, and meet the individual needs of the patient should be prescribed. The present article focuses on issues pertaining to unwanted OC side effects and how they may be minimized by appropriate OC selection, with particular emphasis on those that manifest themselves in ways that are perceptible to users. A

number of studies have suggested that these "physical" side effects are the most common cause of premature discontinuation of oral contraception.

The androgenicity of progestins has received considerable attention in recent years, particularly with the introduction of combination OCs containing progestins with relatively low androgenic activity. Accordingly, much of the following discussion is devoted to the potential role of these newer formulations in reducing OC side effects.

SIDE EFFECTS, DISCONTINUATION, AND PATIENT COMPLIANCE

Clinicians are well aware of the potential effects of OCs on lipid/lipoprotein and carbohydrate metabolism, blood pressure, and hemostatis. Women who use OCs, however, are usually more concerned with avoiding "physical" problems such as weight gain, breakthrough bleeding (BTB), headache, nausea, breast tenderness, and mood changes. Acne and hirsutism, although rarely caused by modern low-estrogen–dose (≤35 μg EE) OCs, are nonetheless important considerations in OC selection because they are often perceived to be related to OCs. These side effects can, in fact, be dramatically reduced by certain formulations. Although physical side effects pose no threat to health, they are frequent causes of OC discontinuation and, probably, subsequent unplanned pregnancy [1].

Some 25% to 50% of women who start oral contraception discontinue using this effective and safe method within the first 12 months after initiation [2]. An analysis by Pratt and Bachrach [1] of data from the 1982 National Survey of Family Growth indicated that most women aged 15 to 44 who stopped using OCs did so on their own initiative; only about one-third had been advised by a doctor to discontinue use. Almost all former users of these older OC formulations, which very often contained higher doses of estrogen than are used today, identified some physical problem connected with OC use as a reason for quitting the method (Figure 1) [1]. The two most common reasons why women stopped taking OCs on their own initiative were weight gain (11.4%) and nausea (10.2%). Headache and menstrual abnormalities also were frequently cited (6.4% and 6%, respectively). Concern about blood clots or heart disease (3.2%) and high blood pressure (1.2%) were given as additional reasons for discontinuation. These figures do not necessarily reflect existing conditions, but in many cases probably indicate patients' fears about the safety of OCs.

Androgenic side effects such as acne and weight gain have also been reported to be a major cause of OC discontinuation [3]. It has been calculated that approximately 25% of women who stop OCs do so because of weight gain [3–5] or acne [3,5], both of which are associated with androgenicity. Additionally, a recent study [6] analyzing OC use in a sample of 6,676 women between the ages of 16 and 30 found

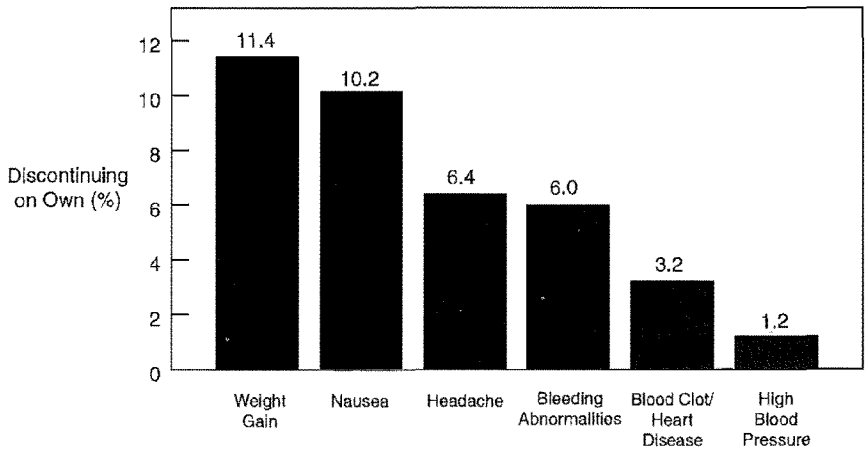

FIG. 1: Physical problems are the main reasons women aged 15 to 44 discontinue use of OCs. Based on data from Pratt, Bachrach [1].

that when hirsutism, another androgenic phenomenon, was present (whether as an actual or perceived side effect), the likelihood of poor compliance with OC regimens was approximately doubled.

Consistent with numerous previous reports, this same study [6] found that poor compliance was also associated with a lack of an established routine for pill-taking, failure to read and understand written materials that come with the OC package, and receiving inadequate information about OCs from their health care provider. Thus, in addition to selecting OC formulations that help minimize unwanted effects, and providing appropriate counseling regarding their possible occurrence and generally transient nature, it is important to ensure that new users understand the basic "mechanics" of OC usage. These aspects are particularly important, since the data from Pratt and Bachrach [1] indicated that 19% of former OC users did not adopt any method after discontinuing oral contraception.

TABLE I
U.S. formulation selections: progestin androgenic activity.

Low	*Medium*	*High*
Norgestimate	Levonorgestrel triphasic	Norgestrel 0.3 mg
Desogestrel	Norethindrone 1.0 mg monophasic or triphasic	Norethindrone acetate 1.5–2.5 mg
Norethindrone 0.4–0.5 mg monophasic	Norethindrone acetate 1.0 mg Ethynodiol diacetate 1.0 mg	Levonorgestrel 0.15 mg

Adapted with permission from Mishell [7].

MINIMIZING PHYSICAL SIDE EFFECTS

To minimize physical side effects, the OC formulation with the lowest doses of progestin and estrogen that will meet the individual needs of the patient should be prescribed. Except for the relatively unusual circumstance in which use of an OC containing 50 µg estrogen may be warranted, most OC users are and should be taking low-estrogen-dose formulations, i.e., containing ≤35 µg EE (40 µg EE in Europe). The relative androgenity of the progestin component has become an issue in selecting among these formulations, because several studies have indicated that OCs with less androgenic potential can minimize some of the physical side effects and adverse metabolic effects traditionally associated with oral contraception.

A consensus conference was convened, therefore, to develop practice guidelines based on the androgenicity of various OC formulations available in the United States. (In European and some other countries, a greater variety of low androgenic OCs is available, including those containing gestodene and dienogest.) OC formulations were categorized on the basis of low-, medium-, or high-androgenic activity of the progestin component (Table 1) [7]. The factors that were taken into account in generating these classifications included the degree to which (1) different progestins bind to androgen receptors, (2) combination OCs containing these progestins increase levels of sex hormone binding globulin (SHBG), and (3) different progestins bind to SHBG, thereby displacing testosterone [8].

Among the signs and symptoms probably attributable to androgenic effects, three—acne, hirsutism, and weight gain—have been emphasized in the literature. Less is known about the relationship, if any, between androgenicity and BTB, headache, nausea, breast tenderness, and mood swings. Further study of the impact of these "androgenic" variables on various physical side effects associated with the use of OCs is needed.

ACNE, HIRSUTISM, AND WEIGHT GAIN

Acne and hirsutism are clearly related to the androgenicity of the progestin component [9]. Several clinical studies have indicated that OC use decreases pre-existing acne and that low-androgenic OCs may benefit hirsute women. A randomized clinical trial by Palatsi and colleagues [10] compared acne scores at study entry and after 6 cycles of OC use in women with pre-existing acne who were treated with two different monophasic OCs, one containing levonorgestrel (0.15 mg) and the other desogestrel (0.15 mg) with the same dose of EE (30 µg). Acne

was scored on a scale ranging from 0 to 3, where 0 equaled clear skin or a few small lesions and 3 equaled severe acne. The results showed that by the sixth cycle of use, the acne had improved significantly in both treatment groups, but the improvement was much greater with the less androgenic progestin, desogestrel (Figure 2) [10]. Even though serum free testosterone fell 60% in both treatment groups, only the desogestrel/EE group showed a significant increase in SHBG, which may account for the difference in acne scores. Other studies have also documented the effectiveness of desogestrel/EE in improving pre-existing acne [11,12].

A beneficial effect on pre-existing acne was observed in a noncomparative European multicenter trial of a monophasic formulation containing norgestimate/EE (0.25 mg/35 μg) [13,14]. Of 41,913 women aged ≤30 years who were enrolled, 4,438 (11%) had acne at study entry. After 6 cycles of OC use, 1,675 of these 4,438 women (37.7%) no longer had acne (Figure 3). In addition, among the total study population, only 1% (439) reported either the

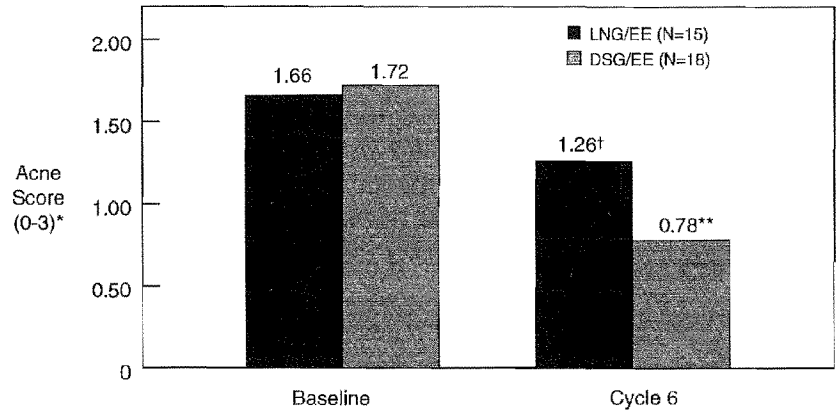

FIG. 2: Acne scores in a comparison trial of levonorgestrel/EE and desogestrel/EE. *0 = clear or a few small lesions; 3 = severe acne. †$P<.01$. **$P<.001$. Based on data from Palatsi et al [10].

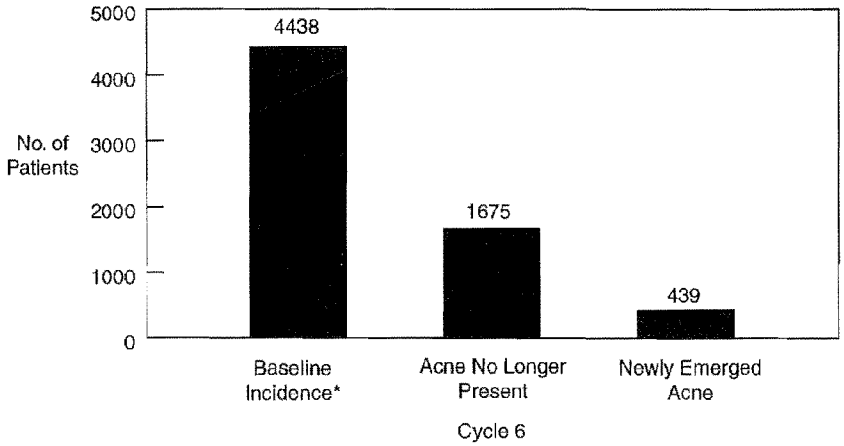

FIG. 3: Acne changes with a norgestimate/EE monophasic OC in women aged ≤30 years. At baseline, 11% of subjects (4,438/41,913) had acne. Adapted with permission from Anderson FD: Selectivity and minimal androgenicity of norgestimate in monophasic and triphasic oral contraceptives. *Acta Obstet Gynecol Scand* 71 (Suppl 156):15–21, 1992. ©1992 Munksgaard International Publishers Ltd., Copenhagen, Denmark. Based on data from Grunwald et al [14].

first appearance of acne or worsening of existing acne over 6 cycles of use. In an open-label study of the norgestimate/35 µg EE formulation in 42,022 women over 6 cycles, the incidence of acne was reduced from 12% pre-treament to 9% after 6 cycles of treatment [15]. Only 1% of patients who did not have acne before treatment reported the appearance of acne during the sixth cycle.

The effects of OC progestins on hirsutism have been most thoroughly studied for desogestrel. In a large study of desogestrel-containing OCs, 499 of 11,605 women had hirsutism before being placed on this preparation [12]. After 6 cycles of OC use, the number of women with pre-existing or newly emerged hirsutism was almost halved. Several other noncomparative studies have documented similar effects on hirsutism after treatment with desogestrel OCs for periods ranging from 5 to 24 months [8].

Many women, especially adolescents, believe that weight gain is caused by the use of OCs, and often give this as the reason for discontinuing oral contraception. OC progestins that most increase SHBG and reduce androgen concentrations might be expected to increase body weight the least [8]. Noncomparative studies of OCs containing norgestimate [13,16] and desogestrel [11,17] have indeed shown that weight gain is rare in women using these formulations, with a mean weight gain of only 1 lb after a whole year of use [13]. Most studies comparing low-androgenic OCs with medium- or high-androgenic preparations, however, have found little or no change in body weight regardless of which formulation is used. Two studies comparing monophasic norgestrel OCs versus monophasic norgestimate did show that discontinuation rates due to weight gain were slightly higher in the norgestrel groups than in the norgestimate groups—1.4% versus 1.0% [16] and 1.54% versus 0.84% [18]—but these findings are difficult to interpret given that diet, age, and other factors that affect body weight are difficult to control in clinical trials. With regard to age, for example, a comparison of a triphasic preparation containing levonorgestrel and a monophasic desogestrel OC found that significant weight gain (approximately 1 kg) occurred with both formulations but only in women under age 20 [19].

The preponderance of evidence, therefore, suggests that OCs cause either no or only slight weight gain. The fact that many women have quite a different perception makes it important to educate patients about weight gain prior to starting them on OCs, so that if they do gain weight, they will not automatically attribute it to the OC.

BREAKTHROUGH BLEEDING

BTB, according to the data reported by Pratt and Bachrach [1], is a common cause of OC discontinuation. BTB usually subsides as time goes by and, in the first 3 or 4 months of OC use, does not require investigation or a change in formulation. The woman just starting OCs should be apprised of these points and should be instructed to take the pills at approximately the same time each day—and not to skip a pill—since there is some evidence that BTB can occur if OC ingestion is delayed by even a few hours. With new-start patients, BTB is often associated with poor compliance. To anticipate this problem, clinicians must counsel each individual patient, which requires knowledge of factors that predict good and poor compliance as well as an understanding of the patient's decision-making processes [20].

BTB is related to the dose, potency, and ratio of the estrogen and progestin in the OC formulation [21] as well as to individual physiologic response. However, information about different OC preparations and how they affect menstrual problems has been confusing [22]. Part of the difficulty is due to differing study populations, cultures, study designs, and the manner in which data were collected and reported. The use of fixed reference periods for quantification of the incidence and severity of vaginal bleeding is clearly important when comparing different OC formulations [23].

Published studies suggest that OCs containing less androgenic progestins and a low estrogen dose are associated with bleeding patterns as acceptable as older low-estrogen-dose (<50 µg EE) formulations [21]. In comparative American studies of 1,473 women using either norgestimate/EE or norgestrel/EE, the daily incidence of BTB and spotting was similar with the two treatment regimens [16]. Another study, which compared a monophasic desogestrel OC with a triphasic levonorgestrel formulation, found cycle control to be equally good for the two preparations [19]. The performance of the gonane progestins (desogestrel, gestodene, norgestimate, and norgestrel) with regard to BTB may be related, at least in part, to their relatively

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