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Menstrual impact of contraception

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Persistent bleeding is a common reason for the discontinuation of contraception. Standard terminology for describing bleeding patterns by reference period is presented. Observed bleeding patterns with oral contraceptives, depot medroxyprogesterone acetate, the levonorgestrel subdermal implant, and intrauterine devices are described. Bleeding days are least with oral contraceptives that are highest in progestin and estrogen potency and dose, but the ratio of the two steroids is also important. Published studies suggest that oral contraceptives containing new nonandrogenic progestins have bleeding patterns as acceptable as older low estrogen formulations. Approaches to the evaluation and treatment of intermenstrual bleeding with contraceptive methods are reviewed. Patient education on expected bleeding patterns is essential to compliance and continuation. (Am J Obstet Gynecol 1994;170:1513-22.)

Key words: Contraception, menstrual cycle, breakthrough bleeding, oral contraception, intermenstrual bleeding

Many contraceptive methods impact on the menstrual cycle and may influence the pattern and amount of bleeding. Persistent bleeding is a common reason for the discontinuation of contraceptive methods and may therefore lead to unwanted pregnancy. A syndrome afflicting new pill users has been described. The patient experiences nausea and as a result skips some pills and then has irregular bleeding, which leads her to stop taking the pills.[1] Contraceptives can have either of two effects on the menstrual cycle: (1) cyclic bleeding continues; oral contraceptives (OCs) as usually prescribed (21 of 28 days) completely suppress the wom-

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0002-9378/94 $3.00 + 0 6/0/53598

en's own ovarian cycle but substitute an artificial cycle because of withdrawal of the hormones on day 21. Intrauterine devices (IUDs) (with the exception of the levonorgestrel-releasing device) do not suppress the ovarian cycle but may have impressive effects on the amount of bleeding. (2) The normal cycle is partially or completely suppressed, and the method does not necessarily induce cyclic bleeding. This type of menstrual effect is seen with progestin-only OCs, the subdermal implants, injectable steroids such as depot medroxyprogesterone acetate (DMPA), and the levonorgestrel-releasing IUD, which contains enough of a potent progestin to inhibit ovulation in some women.

With OCs there is a wide range in bleeding rates between the expected episodes of withdrawal bleeding, depending on the specific formulation.[2] There are difficulties in comparing pills. The terms "breakthrough bleeding" (BTB), defined as bleeding that occurs other than at the time of expected menstruation and sufficient to require the use of pads or tampons, and "spotting," defined as bleeding insufficient to require protection, are commonly agreed on. "Intermenstrual bleeding" includes both BTB and spotting. Generally, the patient is expected to record any bleeding or spotting daily and turn in her report monthly, which may lead to error when patients fill in data forms retrospectively. Unfortunately, as we try to compare OC trials by different groups, we find that definitions are not often given and no standard procedure is followed. For example, some workers report bleeding if a bleeding episode occurs on 1 day, whereas others only count episodes occurring on 2 or more days in succession. The need to study contraceptive use in different cultures introduces further complexity. Any amount of bleeding may be unacceptable in some cultures because a woman may be considered "unclean," not allowed to prepare food or participate in daily activities, and not allowed to have sexual intercourse. In general, pills with high doses of estrogen and progestin have the lowest rates of BTB, but these pills are much less commonly prescribed out of a concern to improve safety and prevent more serious side effects. Producing OC formulations that are lowest in dose and potency but have acceptable bleeding patterns is of great importance. This process would benefit by adoption of common methods and terminology.

The World Health Organization working groups have made serious efforts to define a standard way of reporting bleeding that would be applicable to the study of all contraceptive methods. The "Reference Period Method" is recommended. Events occurring during a specific time period, typically 90 days, are recorded without distinction regarding where or whether they fit into a monthly cycle.[3, 4] A "bleeding day" is a day on which bleeding occurs; a "bleeding episode" is one or more consecutive days during which bleeding occurs. An "interval" is one or more consecutive days with no bleeding, and a "segment" is a bleeding episode that follows an interval with no bleeding. The number of bleeding days, spotting days, episodes of bleeding, their average length, standard deviation of the length, range, minimum, and maximum are reported. Examples of BTB for two triphasic OCs reporting on the basis of both cycle and longer reference periods as recommended by the World Health Organization are given in Figs. 1 and 2.[5]

Determination of rates of intermenstrual bleeding between different OC formulations requires randomized, preferably blinded trials of two or more products compared in a standard fashion by unbiased observers. This is rarely done. One excellent example is a trial of three different 0.050 mg estrogen formulations reported by Ravenholt et al.[6] many years ago. The three OCs were repackaged so that neither patients nor investigators knew the formulation. Patients were contacted daily, and a standard list of questions was administered. BTB was most common in initial cycles and decreased with time. Patients taking the OC of higher progestin potency, which contained dl-norgestrel, had lower rates of BTB. Patients receiving the OCs containing the less potent progestins norethindrone and norethindrone acetate began to bleed toward the end of the pill cycle while still taking the pill; those taking the more potent progestin, dl-norgestrel, did not begin bleeding until cycle day 22, after the OCs had been withdrawn (Figs. 3 and 4). The actual length of withdrawal bleeding was the same for all three OCs. Crossing over was an important feature of this study. Crossing over from the dl-norgestrel pill to either of the others resulted in renewed BTB.

In another trial by independent investigators, Saleh et al.[7] randomly assigned patients to any of the three OC regimens: 1 mg of norethindrone (NET) plus 0.050 mg of ethinyl estradiol (EE) (OC1); 1 mg of NET plus 0.035 mg of EE (OC2); or 0.5 mg of NET plus 0.035 mg of EE (OC3). The study was not blinded. OC3, which had the least of both steroids, had the highest rates of BTB—75% in cycle 1, decreasing to approximately 50% in cycle 8. OC1, the highest dose pill, had the least BTB, but OC2, with the same dose of NET but reduced estrogen, was similar and statistically not separable (Fig. 5). Withdrawal bleeding occurred early in the cycle with OC3, the lowest dose OC (Fig. 6). The investigators also measured blood levels of both steroids and reported baseline and 1-hour slope values at day 21 of the cycle. Although blood levels were higher with the higher dose OCs, no correlation existed between these blood levels and bleeding patterns, and there were large variations between subjects in blood levels of steroids while receiving the same OC.

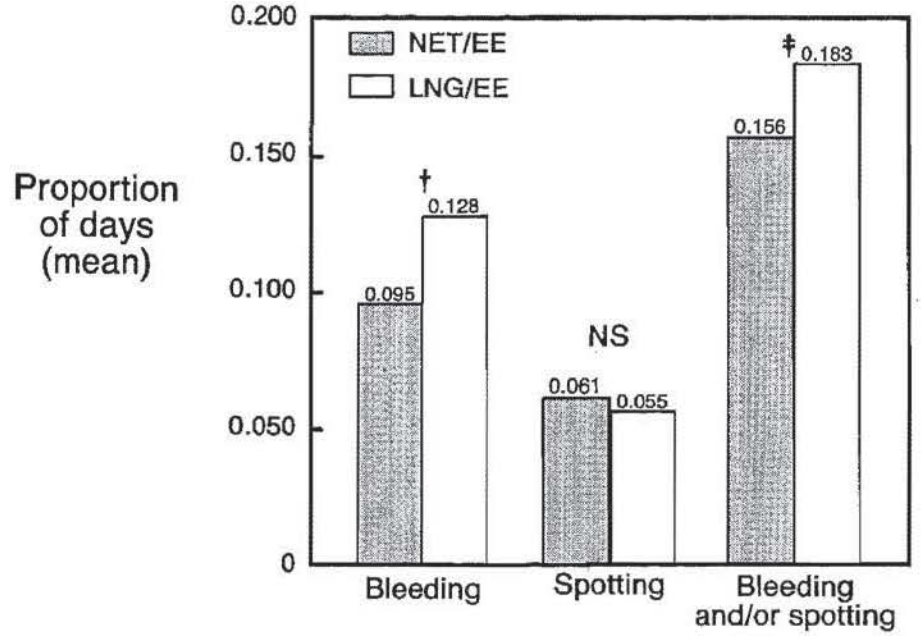

Fig. 1. Analysis by cycle (proportion of all days with bleeding or spotting over 12 cycles). Comparison of two triphasic OCs. *NET,* Norethindrone; *EE,* ethinyl estradiol; *LNG,* levonorgestrel; *NS,* not significant. †p = 0.001; ‡p = 0.018. (From Schwarz BE, et al. Int J Fertil 1992;37:176-82.)

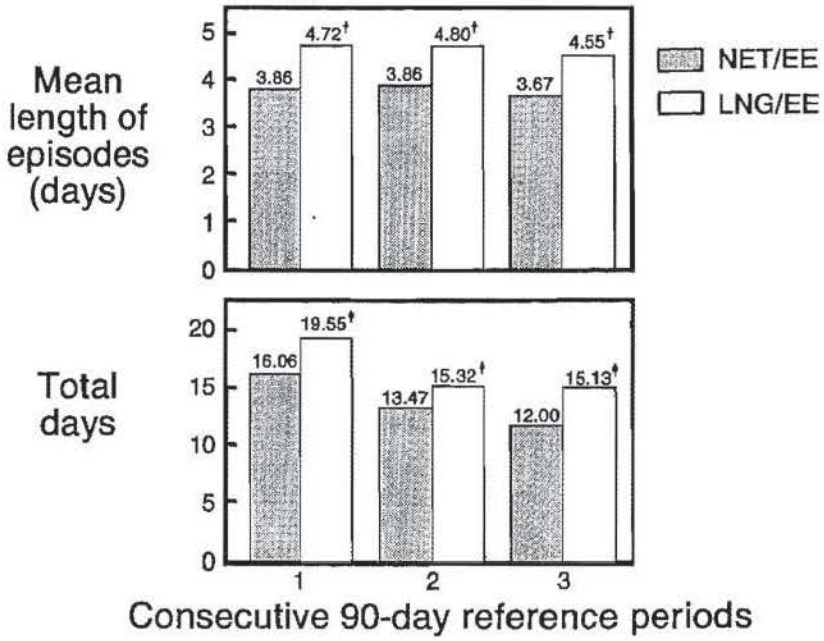

Fig. 2. Analysis by reference period (bleeding and/or spotting over 3 consecutive 90-day reference periods). Comparison of two triphasic OCs. *NET,* Norethindrone; *EE,* ethinyl estradiol; *LNG,* levonorgestrel. †p = 0.001; ‡p = 0.013. (From Schwarz BE, et al. Int J Fertil 1992;37:176-82.)

In addition to dose and potency of the two sex steroids, the ratio of the two may also impact bleeding. Lawson et al.[8] studied seven different dosage combinations of norgestimate and ethinyl estradiol in non-blinded study. Results are expressed in three-dimensional response surfaces (Figs. 7 to 9). In this study, spotting and BTB were combined. Bleeding was least frequent at the higher doses of either estrogen or

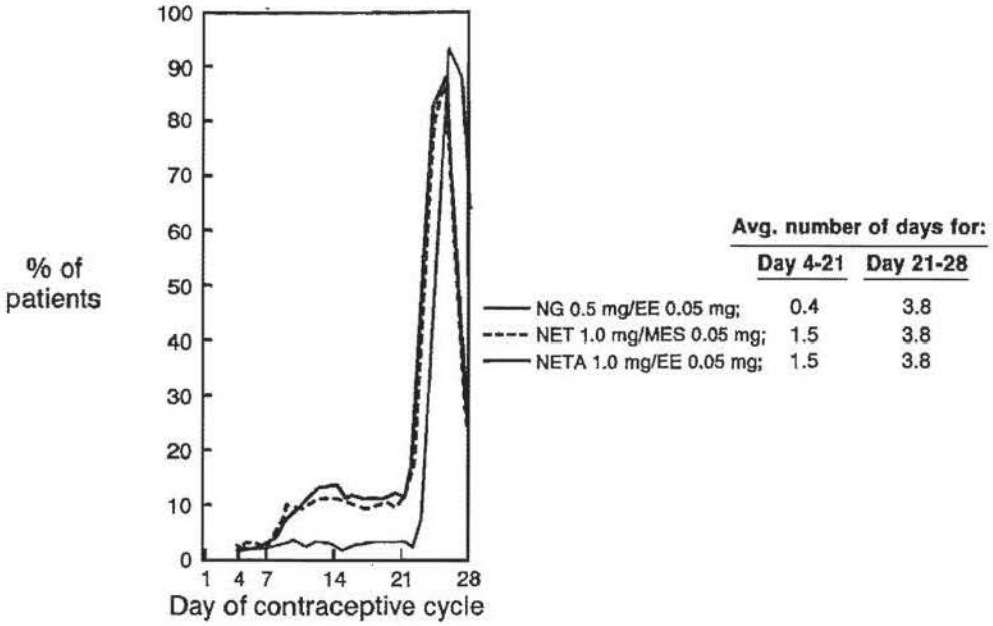

Fig. 3. Cycle day of onset of vaginal bleeding with three different 0.050 mg OCs averaged for first three cycles. A double-blind crossover study of NG/EE, NET/MES, and NETA/EE. *NG,* Norgestrel; *EE,* ethinyl estradiol; *NET,* norethindrone; *MES,* mestranol; *NETA,* norethindrone acetate. (From Ravenholt RT, et al. Adv Plann Parent 1978;12:222-39.)

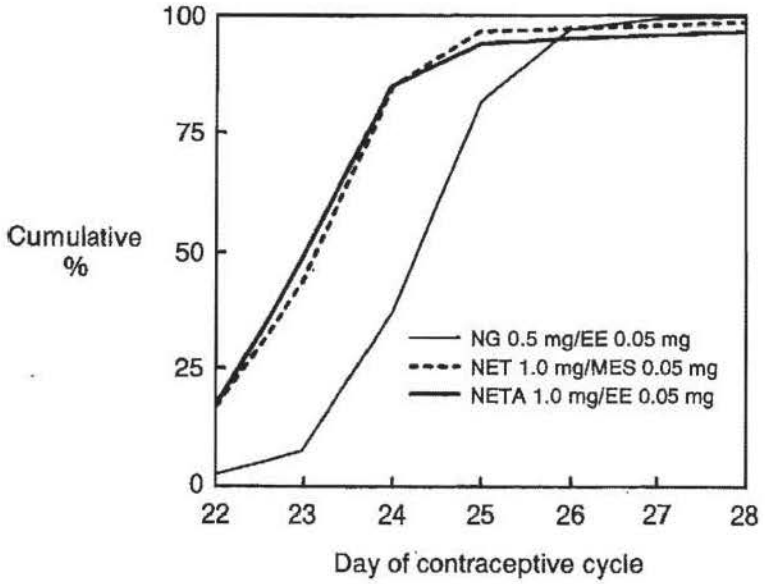

Fig. 4. Percentage of patients with withdrawal bleeding by cycle day with three different 0.050 mg OCs averaged for first three cycles. (From Ravenholt RT, et al. Adv Plann Parent 1978;12:222-39.)

progestin but remained acceptably low over a range of reduced doses of estrogen and progestin, provided similar ratios of estrogen to progestin were maintained (Fig. 7). This would lead to the expectation that one could decrease BTB by increasing either hormone. Nausea and vomiting were largely related to estrogen dose and decreased as estrogen was decreased, independent of progestin dosage (Fig. 8). The pregnancy rate was highest at the lowest doses of both hormones but was least at an intermediate dose and decreased as the progestin dose increased (Fig. 9).

In introducing new formulations it is important to compare the effect on bleeding patterns in a randomized fashion to a standard formulation with an ac-

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