Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials*

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BACKGROUND: With the recent US Food and Drug Administration approval of a combination oral contraceptive that causes a withdrawal bleed every 3 months instead of monthly, avoidance of menstruation through extended or continuous administration (>28 days of active pills) of combined oral contraceptives may become more commonplace for reasons of personal preference rather than limited to treatment of menstrual-associated medical disorders.

METHODS: The review aimed to compare contraceptive efficacy, compliance, continuation, satisfaction, bleeding profiles, and menstrual symptoms of combined oral contraceptives with continuous dosing (>28 days of active pills) versus traditional cyclic dosing (21 days of active pills and 7 days of placebo). We searched five computerized databases as well as reference lists of relevant articles for randomized controlled trials (RCT) using continuous or extended combined oral contraceptives for contraception. Two reviewers independently extracted data from eligible articles. RESULTS: Six RCT met inclusion criteria and were of good quality. Contraceptive efficacy and compliance were similar between groups. Discontinuation overall, and for bleeding problems, was not uniformly higher in either group. When studied, participants reported high satisfaction with both dosing regimens. Five out of the six studies found that bleeding patterns were either equivalent or improved with continuous-dosing regimens. The continuous-dosing group had greater improvement of menstrual-associated symptoms (headaches, genital irritation, tiredness, bloating, and menstrual pain). CONCLUSIONS: The variations in pill type and time-interval for continuous dosing make direct comparisons between regimens unfeasible. To allow for comparisons, future studies should choose a previously researched pill and dosing regimen. More attention needs to be directed towards participant satisfaction and menstruation-associated symptoms.

Key words: continuous or extended dosing regimen/oral contraceptives/randomized controlled trials/review

Introduction

Is monthly menstruation necessary? In hunter-gatherer times, women had infrequent menstruations because they often had closely-spaced pregnancies; breastfed their infants for long intervals (which suppresses ovulation and menstruation) and died before reaching menopause. Prehistoric women had as few as 50 menstruations per lifetime, whereas the modern woman has ~450 (Thomas and Ellertson, 2000).

The traditional 28 day cycle (21 days of active pills with 7 days of placebo, which allows a withdrawal bleed) produced by birth control pills has no basis in biology. Indeed, the developers of the first combined oral contraceptives (COC) adopted this regimen to mimic naturally occurring menstrual cycles. This decision was based on cultural and social pressures of the 1950s rather than on biological considerations (Coutinho and Segal, 1999; Gladwell, 2000).

The avoidance of menstruation through extended or continuous administration (>28 days of active pills) using COC has gained legitimacy through its therapeutic uses. For example, continuous use of COC has successfully treated endometriosis, dysmenorrhea, and menstrual-associated symptoms (Sulak et al., 1997, 2000; Vercellini et al., 2002; Kwiecien et al., 2003). In addition, the US Food and Drug Administration (FDA) recently approved the marketing of a monophasic levonorgestrel and ethinyl estradiol COC in an extended regimen.
COC enable women to avoid menstruation for personal reasons as well. Avoidance of menstruation through continuous dosing of COC has several potential advantages, including improved adherence to the pill regimen, less interference with daily activities or special events, decreased expense for feminine hygiene products, and less menstruation-related absenteeism from work or school (Schwartz et al., 1999; Miller and Notter, 2001; Cote et al., 2002; Miller and Hughes, 2003). Some women, though, worry about the possibility of menstrual ‘build-up’, creation of an ‘unnatural’ state, and the possibility of pregnancy with ‘missed’ periods. However, with reassurance regarding safety, most women would prefer to delay or never have a period (Rutter et al., 1988; Tonkelaar and Oddens, 1999; Glasier et al., 2003). The preference for amenorrhoea has been documented in research among women from both developed and undeveloped countries except for black women in Africa (Rutter et al., 1988; Glasier et al., 2003; Wiegratz et al., 2004).

The physiology of COC and their impact on the hypothalamic–pituitary–ovarian axis support the safety of continuous administration. COC inhibit FSH and LH, which in turn prevent follicular development, growth of the endometrial lining, and ovulation. The bleeding that occurs during the pill-free interval is not due to endometrial ‘build-up’ but to hormone withdrawal (Speroff et al., 1999). Continuous pill administration maintains a progesterin effect resulting in a thin endometrium. In addition to endometrial lining suppression, continuous administration also appears to suppress pituitary activity more effectively than cyclic administration does (Ruchhoft et al., 1996). The long-term health effects have not been documented.

New regimens for COC need to be evidence-based. Hence, this review examines the randomized controlled trials (RCT) comparing continuous (or extended) regimens versus the traditional cyclic regimen of COC.

Materials and methods

Criteria for trial eligibility

All RCT in any language comparing continuous or extended cycle (>28 days of active pills) versus traditional dosing (21 days of active pills and 7 days of placebo) of COC for contraception were eligible for review. The study populations had to be comprised of reproductive age women using COC for contraceptive purposes. COC for treatment of conditions such as endometriosis were excluded.

The types of outcomes extracted from the studies included participant satisfaction, study discontinuation (overall, bleeding problems, and adverse events), participant adherence/compliance, pregnancy, endometrial thickness and/or endometrial histology, evaluation of bleeding patterns, improvement of menstrual-associated symptoms, and adverse events.

Search strategy for trial identification

We searched the computerized databases of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and POPLINE for trials of continuous or extended cycle versus cyclic use of COC for contraception. We wrote to the corresponding authors of published trials to seek other trials we may have missed. We also searched the references of the published trials identified for inclusion.

Method of data extraction and analysis

The primary reviewer (A.E.) evaluated the titles and abstracts identified from the literature searches and assessed relevant articles for potential inclusion. Continuous COC were defined as the use of active pills for >28 days. After extraction by both the primary and secondary reviewers to ensure accuracy, the data from the eligible trials were entered into RevMan 4.2. RevMan is an information management system used by the Cochrane Collaboration that assists in organizing and analysing data (http://www.cc-ims.net/). Peto odds ratios (Peto OR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes. Weighted mean differences (WMD) were used for continuous outcomes. Data in the present review are based on the analytical method (e.g. intention-to-treat, per-protocol) used in the trial report.

Results

Description of studies

The search strategy identified a total of 17 publications. Six RCT met inclusion criteria (Table I) (Cachrimanidou et al., 1993; Coutinho et al., 1995; Miller and Notter, 2001; Anderson and Hait, 2003; Kwiecien et al., 2003; Miller and Hughes, 2003). Kwiecien et al. (2003) and Miller and Hughes (2003) used the same COC formula of 20 μg ethinyl estradiol/100 μg levonorgestrel for both their continuous and traditional regimens. The remainder used a variety of formulations: 30 μg ethinyl estradiol/150 μg desogestrel, (Cachrimanidou et al., 1993), 50 mg ethinyl estradiol/250 mg levonorgestrel (Coutinho et al., 1995), 30 μg ethinyl estradiol/300 μg norgestrel (Miller and Notter, 2001), and 30 μg ethinyl estradiol/150 μg levonorgestrel (Anderson and Hait, 2003). While all eligible studies defined cyclic administration as a 28 day cycle (21 days of active pills with 7 days of placebo), the length of the continuous administration varied: 70 days for five cycles (Cachrimanidou et al., 1993), 365 days (Coutinho et al., 1995) 49 days for four cycles (Miller and Notter, 2001), 91 days for four cycles (Anderson and Hait, 2003), 168 days (Kwiecien et al., 2003) and 336 days (Miller and Hughes, 2003).

COC were given orally in all of the studies except for the trial by Coutinho (1995) et al. in which the vaginal route was used. Analysis and reporting of bleeding patterns varied in each study. Cachrimanidou et al. (1993) defined ‘spotting’ as requiring no or only one sanitary napkin per day and ‘bleeding’ as requiring at least two sanitary pads per day. Diaries were analysed in 70 day blocks for continuous use and 84 day blocks for cyclic use (withdrawal bleeding days were analysed separately from bleeding and spotting days). Several authors (Coutinho et al., 1995; Miller and Notter, 2001; Anderson and Hait, 2003; Kwiecien et al., 2003; Miller and Hughes, 2003) evaluated bleeding using definitions adapted from the World Health Organization (WHO) (Coutinho et al., 1995; Suvisaari and Lahteenmaki, 1996; Miller and Notter, 2001; Anderson and Hait, 2003; Kwiecien et al., 2003; Miller and Hughes, 2003). The WHO bleeding definitions state that spotting is

References

[References provided in the original document are not included in this text.]

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Table 1. Description of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tr>
<td>Anderson et al. (2003)</td>
<td>Randomized controlled trial. Computer-generated randomization through a treatment allocation centre. Open label. Multicentre trial (47 US sites). Funded by Barr Labs</td>
<td>682 participants aged 18–40 years. The inclusion criteria were healthy, at risk for pregnancy, English-speaking, and no COC contraindications</td>
<td>28 day (n = 226) versus 91 day (n = 456) cycles for 1 year. COC type: 150 μg levonorgestrel and 30 μg of ethinyl estradiol</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 364 day blocks. Secondary outcomes included compliance and patient acceptance. Bleeding definitions used: ‘spotting’ requires no protection and ‘bleeding’ requires protection</td>
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<td>Cachrimanidou et al. (1993)</td>
<td>Randomized controlled trial. Method of randomization not reported. Sealed envelopes were used for allocation. Open label. Multicentre trial (three Swedish sites). Funded by Organon</td>
<td>294 participants aged 18–39 years. Inclusion and exclusion criteria were unclear except for no COC contraindications</td>
<td>28 day (n = 96) versus 70 day (n = 198) cycles for 1 year. COC type: 150 μg desogestrel and 30 μg ethinyl estradiol</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 70 day blocks for continuous dosing and 84 day blocks for cyclic. Secondary outcomes included body weight and blood pressure changes, menstrual-associated symptoms, and patient satisfaction. Bleeding definitions used: ‘spotting’ does not require protection or at most on pad/day, ‘bleeding’ requires ≥2 pads/day</td>
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<tr>
<td>Coutinho et al. (1995)</td>
<td>Randomized controlled trial. Computer-generated randomization. Allocation concealment was not reported. Open label. Vaginal dosing of COC. Multicentre trial (Brazil, China, Egypt). No external funding. SE reported for mean number of bleeding/spotting days; however, it appears to be SD and that is how it was used in this analysis</td>
<td>900 participants of reproductive age. Inclusion and exclusion criteria were not stated</td>
<td>8 day (n = 454) versus 1 year (n = 446) cycles for 1 year. COC type: 250 μg levonorgestrel and 50 μg ethinyl estradiol</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 90 day blocks. Secondary outcomes included changes in weight, blood pressure, red blood cell count, haematocrit, and haemoglobin. Bleeding definition used: ‘spotting’ requires no protection and ‘bleeding’ requires protection</td>
</tr>
<tr>
<td>Kwiecien et al. (2003)</td>
<td>Randomized controlled trial. Computer-generated randomization. Sealed opaque envelopes for allocation. Open label. One centre in Portland, Oregon. No external funding.</td>
<td>32 participants aged 18–50 years. Inclusion criteria were healthy, at risk for pregnancy, English-speaking, and no COC contraindications</td>
<td>28 day (n = 16) versus 168 day (n = 16) cycles for 6 months. COC type: 100 μg levonorgestrel and 20 μg ethinyl estradiol</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 28 day blocks. Secondary outcomes included menstrual-associated symptoms, patient satisfaction, and endometrial stripe by transvaginal ultrasound. Bleeding definitions used: ‘spotting’ defined as no protection needed and ‘bleeding’ as needing sanitary protection</td>
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<tr>
<td>Miller and Notter (2001)</td>
<td>Randomized controlled trial. Computer-generated randomization. Allocation concealment performed using sequentially numbered envelopes with carbon paper inside, opened after the women signed the envelope flap. Open label. Four clinical sites in Seattle, Washington. Funded by a non-profit grant.</td>
<td>90 participants aged 18–45 years. Inclusion criteria were no COC contraindications and do not desire pregnancy for 1 year</td>
<td>28 day (n = 44) versus 49 day (n = 46) cycles for 1 year. COC type: 300 μg norgestrel and 30 μg ethinyl estradiol</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 84 day blocks. Secondary outcomes included use of hygiene products, patient compliance, and menstrual-associated symptoms. Bleeding definitions used: ‘spotting’ requires no protection and ‘bleeding’ requires protection</td>
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<tr>
<td>Miller and Hughes (2003)</td>
<td>Randomized controlled trial. Computer-generated randomization. Allocation concealment performed using sequentially numbered sealed brown bags holding study medication. Open label. One site in Seattle, Washington. Funded by Wyeth</td>
<td>79 participants aged 18–45 years. Inclusion criteria were no OCP contraindications. No uterine or cervix abnormalities, no use of contraceptive injection 6 months prior to study start, and no intention to become pregnant for 1 year</td>
<td>28 day (n = 40) versus 336 day (n = 39) cycles for 1 year. COC type: 100 μg levonorgestrel and ethinyl estradiol 20 μg</td>
<td>The primary outcome measured was bleeding profiles. Bleeding profiles were analysed in 84 day blocks. Secondary outcomes included patient satisfaction and compliance, weight and blood pressure changes, and endometrial stripe by vaginal ultrasound. Bleeding definitions used: ‘spotting’ needing no protection and ‘bleeding’ needing protection</td>
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COC = combined oral contraceptive.

bloody vaginal discharge that does not require protection, and that bleeding does require protection. Coutinho et al. (1995) analysed diaries in 90 day blocks (withdrawal bleeding days were included). Both trials by Miller and Notter (2001) and Miller and Hughes (2003) analysed diaries in 84 day blocks or trimesters (withdrawal bleeding days were included) (Miller and Notter, 2001; Miller and Hughes, 2003). In the earlier trial by Miller and Notter (2001), since 49 days does not divide equally into an 84 day block, one withdrawal bleeding week was included in the first and fourth trimesters and two in the second and third trimesters. However, the traditional dosing group was analysed in three 28 day cycles, each containing one withdrawal week. Kwiecien et al. (2003) analysed diaries in 28 day blocks but also provided information that allowed us to
analyse the data in 84 day blocks (withdrawal bleeding days were included). Anderson and Hait (2003) analysed diaries in 364 day blocks (withdrawal bleeding days included).

Most enrolled women were ‘switchers’ (those who were on COC during the cycle prior to entering the study) versus ‘new starts’ (never users of COC). Cachrimanidou et al. (1993), Miller and Notter (2001), Anderson and Hait (2003) and Miller and Hughes (2003) reported a ≥60% percentage of COC switchers in both the continuous and traditional groups. Coutinho et al. (1995) and Kwiecien et al. (2003) did not specify the percentage of switchers per group, but Coutinho et al. reported that 91% of study participants were on some type of birth control prior to study entry and Kwiecien et al. only reported prior use of COC [traditional group 10/16 (62.5%); continuous group 11/16 (68.7%)].

Endometrial safety of continuous COC was monitored in the trials by Kwiecien et al. (2003) and Miller and Hughes (2003) by measuring endometrial thickness with a vaginal probe ultrasound and/or endometrial biopsy. Both studies defined a normal endometrial thickness to be <5 mm while on COC, as this is the threshold value for concern for abnormal pathology in postmenopausal women (Goldstein et al., 1990).

Methodological quality of included studies
Information regarding randomization and allocation concealment obtained from the publications and written correspondence with the authors proved these two areas to be adequate in most included studies. Five studies reported the use of computer-generated randomization schemes, while Cachrimanidou et al. (1993) failed to report the method of randomization. Allocation concealment was by sequential, sealed, opaque envelopes (Miller and Notter, 2001; Kwiecien et al., 2003), sealed opaque envelopes (Cachrimanidou et al., 1993), sequential, sealed brown bags (Miller and Hughes, 2003), and a treatment allocation centre (Anderson and Hait, 2003). Coutinho et al. (1995) provided no information on concealment techniques. Once allocation to treatment groups had occurred, the treatment was unblinded for both participants and investigators in all of the studies. Kwiecien et al. (2003) and Miller and Hughes (2003) used an intent-to-treat analysis. Miller and Notter (2001) excluded participants who did not complete full trimesters (84 day blocks) of study participation. Anderson and Hait (2003) excluded patients from Pearl index calculations who did not adhere to their assigned pill-dosing regimen. Coutinho et al. (1995) excluded data from participants in the continuous group who decided to have a withdrawal bleed. The analytic approach in the trial by Cachrimanidou et al. (1993) was unclear.

Study findings
Bleeding patterns were the main outcomes for the six studies. Most trials showed either no difference between groups or less bleeding and/or spotting with continuous dosing of COC. Women in the continuous arm in the Coutinho et al. trial reported a mean 10.7 fewer total bleeding days (95% CI -11.3 to -10.04) in the first trimester than the cyclic group (Coutinho et al., 1995). WMD for the second to fourth trimesters were similar. (Note that we assumed that the SD were misidentified in the report as SE since the latter statistics were improbable.) Miller and Notter (2001) found no statistically significant differences in the mean number of bleeding or spotting days for the four trimesters with one exception: the continuous group had a mean of 4.5 and 3.9 fewer bleeding days (95% CI -7.1 to -1.9 and -6.8 to -1.04) in the first and third trimesters, respectively, than the cyclic dosing group. Anderson and Hait (2003) evaluated bleeding patterns over the entire 364 day study period and reported no significant differences between groups for the mean bleeding plus spotting days. However, the continuous arm had fewer bleeding-only days (WMD -14.3; 95% CI -17.7 to -11.0). Kwiecien et al. (2003) found no difference between groups in the mean total bleeding days (bleeding plus spotting) and mean spotting days in either of the study’s two (84 day) trimesters, but the continuous group had fewer mean bleeding-only days than the cyclic administration group for both the first (WMD -7.7; 95% CI -14.0 to -1.5) and the second trimester (WMD -8.9; 95% CI -12.8 to -4.9). No clear picture regarding bleeding patterns emerged for the Miller and Hughes trial (2003). The groups did not differ significantly for the mean total bleeding days during the four (84 days) trimesters. While the cyclic group had fewer mean spotting days during the first two trimesters (but not the last two trimesters), women in this group had more mean bleeding days for the four trimesters. Finally, Cachrimanidou et al. (1993) analysed bleeding outcomes differently from the five previous studies in that they analysed bleeding during the withdrawal week separately. Bleeding associated with the withdrawal week was decreased for the 70 day cycle compared to 28 day cycle, but for mean bleeding and mean spotting days (analysed over 70 days for the 70 day cycle and 84 days for the 28 day cycle), there were more days for the extended cycle group (P < 0.05).

Participant satisfaction was not measured consistently in the six studies. Cachrimanidou et al. (1993) obtained satisfaction data only from ‘ever-users’ of contraception in the extended cycle arm (63% of whom reported a preference for an extended cycle). Coutinho et al. (1995) did not report satisfaction outcomes except for non-medical reasons for study discontinuation (e.g. dislikes method). Both articles by Miller used a five-point Likert scale to determine participant satisfaction, but neither trial found a significant difference in satisfaction between study arms (Miller and Notter, 2001; Miller and Hughes, 2003). Anderson and Hait (2003) reported that participants from both study groups expressed a preference for fewer menstrual periods. Kwiecien et al. (2003) used 10 cm visual analogue scales (VAS) with the anchors ‘unsatisfied’ and ‘very satisfied’ to determine participant satisfaction. Participants from both groups reported being ‘very satisfied’ (P = 1.0).

Overall study discontinuation (including lost to follow-up) was lower in traditional 28 day cycles compared to extended cycles in one study (OR 1.6; 95% CI 1.2 to 2.3) (Anderson and Hait, 2003). Otherwise, the groups did not differ in overall study discontinuation [OR 1.4, 95% CI 0.9 to 2.4 (Cachrimanidou et al., 1993); OR 1.0, 95% CI 0.7 to 1.5 (Coutinho et al., 1995); OR 0.7, 95% CI 0.3 to 1.6 (Miller and Notter, 2001); OR 0.3, 95% CI 0.04 to 2.6 (Kwiecien et al., 2003); OR 0.5, 95% CI 0.2 to 1.5 (Miller and Hughes, 2003)]. In regard to study
discontinuation due to bleeding problems, Anderson and Hait (2003) and Cachrimanidou et al. (1993) had more discontinuations in the 28-day cycle arm with odds ratios of 3.0 (95% CI 1.5 to 5.9) and 3.6 (95% CI 1.6 to 8.2), respectively. The remaining four studies showed no statistically significant differences between groups.

Participant adherence data were reported in three studies. Miller and Notter (2001), who defined compliance by the number of missed or late pills, found no difference between groups (28 day = 1.3 and 49 day = 1.2,  P = 0.5). Anderson and Hait (2003) determined compliance as the percentage of total study days when participants took the designated pill for the given day. Compliance rates for both groups were not different (OR 0.7; 95% CI 0.3 to 1.3). Miller and Hughes (2003) defined compliance as missing three or more pills during the first and last trimesters (84-day interval) of the study. No statistically significant difference between groups in either trimester was found.

The risk of pregnancy did not differ between regimens except in one trial (Coutinho et al., 1995) that showed fewer pregnancies in the continuous administration group (OR 0.1; 95% CI 0.0 to 1.0).

Kwiecien et al. (2003) and Miller and Hughes (2003) assessed the endometrium by ultrasound and/or endometrial biopsy. In the Kwiecien et al. (2003) trial, 14 women in the continuous administration group (n = 16) volunteered to undergo endometrial stripe assessments by ultrasound; the mean thickness was 3.3 mm (SD 0.73, range 2–4 mm). No participant met criteria for biopsy (stripe >5 mm). Miller and Hughes (2003) evaluated a volunteer subset of the study (28-day cycles, n = 7; 336-day cycles, n = 9), and two participants in the 336-day cycle group underwent assessments because of prolonged bleeding. All evaluations were performed during cycle nine. All endometrial stripe measurements were <5 mm and no evidence of hyperplasia was found on biopsy.

Only three studies reported data on menstruation-associated symptoms, which were collected with participant diaries. Cachrimanidou et al. (1993) monitored the increased or decreased frequency of headaches, nervousness, nausea, dizziness, depression, acne, and dysmenorrhea. The continuous-dosing arm showed benefit for headache frequency (P < 0.05), although no other important differences in other menstruation-associated symptoms were found. Miller and Notter (2001) monitored the presence and severity of cramping, tiredness, headache, breast tenderness, and genital irritation. Genital irritation (P = 0.02), headache (P = 0.04), and tiredness (P = 0.05) were less severe in the 49-day cycle group than in the cyclic group. Kwiecien et al. (2003) collected data on headache, nausea, bloating, breast tenderness, pre-menstrual syndrome, and menstrual pain. No significant difference was found between groups except that women in the continuous group were less likely to report bloating days (WMD -11.0; 95% CI -19.8 to -2.2) and menstrual pain (WMD -11.5; 95% CI -18.4 to -4.5) than those in the continuous regimen.

No serious adverse events related to the study medication or regimen were reported in five trials (Cachrimanidou et al., 1993; Coutinho et al., 1995; Miller and Notter, 2001; Kwiecien et al., 2003; Miller and Hughes, 2003). Anderson and Hait (2003) reported three adverse events likely related to study drug, including a pulmonary embolism (extended cycle), cholecystitis (28-day cycle), and an exacerbation of pre-existing depression (28-day cycle). The adverse event data also showed fewer headaches in the continuous group than the cyclic group (OR 0.7; 95% CI 0.5 to 1.0).

Discussion

Evidence from published RCT comparing COC dosed continuously (>28 days of active pills) to traditional monthly cyclic dosing (21 days of active pills and 7 days of placebo) overall is of good quality. However, variations in pill type and regimen length for continuous dosing make direct comparisons between studies unfeasible.

Most bleeding outcomes showed either no statistically significant difference between groups or less bleeding and/or spotting with continuous dosing of COC. Only one trial (Cachrimanidou et al., 1993) consistently had fewer bleeding and spotting days for 28-day cycles, but the authors did not include withdrawal bleeding and spotting days, which were lower for extended cycles.

The few studies that examined menstruation-associated symptoms found improvements in the continuous-dosing group for several outcomes, including headaches (Cachrimanidou et al., 1993; Miller and Notter, 2001), genital irritation (Miller and Notter, 2001), tiredness (Miller and Notter, 2001), bloating (Kwiecien et al., 2003), and menstrual pain (Kwiecien et al., 2003).

Overall discontinuation rates were lower in 28-day cycles for one trial (Anderson and Hait, 2003) but rates were similar between groups for the remaining five studies. Discontinuation rates due to bleeding problems were no different for four studies but were lower for the 28-day cycle group in two studies (Cachrimanidou et al., 1993; Anderson and Hait, 2003).

Participant satisfaction may be a proxy for compliance to pill regimen. Only three studies examined participant satisfaction (Miller and Notter, 2001; Kwiecien et al., 2003; Miller and Hughes, 2003), two of which had compliance outcomes (Miller and Notter, 2001; Miller and Hughes, 2003). Satisfaction was high in both 28-day and extended cycles for all three studies. No statistically significant difference in compliance rates was seen between 28-day and extended cycles in either study (Miller and Notter, 2001; Miller and Hughes, 2003).

Although the trial by Anderson and Hait (2003) showed no substantial difference in compliance rates, they did not measure satisfaction appropriately for the two groups. Furthermore, measurements of compliance based on participant diaries have questionable validity (Potter and Oakley, 1996).

The trial numbers were too small to address either contraceptive efficacy or rare adverse events. Overall, oral contraceptives are safe and effective, and continuous pill use is a reasonable approach to oral contraception. In future studies, more attention needs to be directed towards participant satisfaction and menstruation-associated symptoms.

In conclusion, COC given continuously (>28 days of active pills) and traditional cyclic dosing (21 days of active pills and 7 days of placebo) have similar participant satisfaction, discontinuation rates (overall and for bleeding problems), and participant satisfaction appropriately for the two groups. Further, measurements of compliance based on participant diaries have questionable validity (Potter and Oakley, 1996).
adherence. Menstruation-associated symptoms may be improved with continuous dosing. Bleeding patterns appear to be equivalent between regimens or improved with continuous administration. The trial sizes were inadequate to assess differences in safety and contraceptive effectiveness in the general population. Continuous dosing of COC is a reasonable approach for women without contraindications to COC.

More attention needs to be directed towards participant satisfaction, menstruation-associated symptoms, and long-term health effects of continuous administration. RCT are not useful for studying potential long-term sequelae, so case-control studies or post-marketing surveillance will be required. Trials should report their methods and results in the manner consistent with CONSORT guidelines (Moher et al., 2001).

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