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Review article

Effective use of hormonal contraceptives☆ Part I: Combined oral contraceptive pills

Kathryn M. Curtis[a,*], Camaryn E. Chrisman[b], Anshu P. Mohllajee[a], Herbert B. Peterson[c,d]

[a]World Health Organization Collaborating Center in Reproductive Health, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA
[b]Wake Forest University School of Medicine, Winston–Salem, NC 27157, USA
[c]Department of Maternal and Child Health, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[d]Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

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Abstract

This systematic review examines evidence regarding when during the menstrual cycle a woman can initiate combined oral contraceptive (COC) use and what can be done if a woman misses COCs. We searched the MEDLINE and EMBASE databases for articles published from 1966 to March 2005 related to COC initiation and to the effects of late or missed COCs. We identified 11 studies related to COC initiation and 25 studies related to the effects of missed pills. Evidence from these studies suggested that taking hormonally active pills for 7 consecutive days prevents normal ovulation and that initiating COCs through Day 5 of the menstrual cycle suppresses follicular activity. Studies on the effects of missed COCs generally showed that the risk of ovulation is greatest when the pill-free interval lasts >7 days. Limitations of this body of evidence include small sample sizes that may not reflect variation in larger populations, lack of a standard measurement of ovulation and difficulty in discerning how ovulation resulting from late or missed COCs corresponds to the risk of conception.

Keywords: Contraception; Time factors; Follicular development; Ovulation; Systematic review

1. Introduction

When combined oral contraceptives (COCs) were first marketed in 1960, many expected that all future pregnancies would be planned pregnancies. Yet, although COCs are nearly 100% effective if taken daily, an 8% typical use failure rate in the first year of use reflects the fact that pills are frequently missed [1]. In fact, surveys from around the world have reported that as many as 60% of COC users report irregular use [2]. In the United States in 1995, 15.5% of COC users reported missing one pill and another 13.3% reported missing two or more pills in the past 3 months [3].

Clinicians who provide family planning services face daily challenges in helping women and men initiate contraceptive use and continue to use their chosen contraceptive method successfully. Clinical decisions about when during the menstrual cycle a woman can start hormonal contraception are chiefly made in the context of concerns regarding whether the woman may already be pregnant and the risk that she will become pregnant during that menstrual cycle. The latter consideration, in turn, depends on how the timing of COC initiation relates to the mechanisms of action for pregnancy prevention, particularly the prevention of ovulation. Decisions about when to start hormonal contraception are also affected by how side effects, particularly vaginal bleeding, may vary with the timing of initiation. In addition, clinicians often must advise women about what to do after missing pills, as well as help them select the most effective pill-taking regimen. A recent commentary suggested decreasing the traditional 7-day pill-free interval to increase the effectiveness of COCs [4].

In April 2004, the World Health Organization (WHO) convened a working group of international family planning experts to develop and revise evidence-based practice recommendations that would assist in addressing these

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* Corresponding author. Tel.: +1 770 488 6397; fax: +1 770 488 6391.
E-mail address: kmc6@cdc.gov (K.M. Curtis).

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questions and concerns. To provide this working group with the best available information about when a woman can initiate COCs and what she can do if she misses COCs, we conducted systematic reviews of the relevant evidence. In this report, we provide the evidence obtained through our systematic reviews, as well as the WHO recommendations that were derived in part from this evidence, with respect to two research questions: (1) When can a woman start COCs? and (2) What can a woman do if she misses COCs? This review also includes evidence identified since the 2004 meeting through March 2005.

2. Materials and methods

We searched the MEDLINE and EMBASE databases for reports on primary research published in peer-reviewed journals from 1966 through March 2005, in any language, that related to the timing of COC initiation or to missed COCs (Appendix A). Using reference lists from articles identified by our search as well as from key review articles, we then conducted hand searches to identify any additional study relevant to this review. We did not attempt to identify unpublished articles or abstracts from scientific conferences.

2.1. Study selection, study quality and data synthesis

We identified 238 articles from MEDLINE and 612 from EMBASE relevant to the initiation of COCs and 123 from MEDLINE and 296 from EMBASE regarding missed COCs. Following a review of the article titles and abstracts, as well as the full articles when appropriate, we identified 11 articles that specifically examined the timing of initiation of COCs and 25 that examined risk of ovulation following missed COCs. We summarized and systematically assessed the evidence through the use of standard abstract forms [5] and graded the evidence for each research question, based on the criteria of the United States Preventive Services Task Force (Appendix B) [6]. Because of the heterogeneity of study designs and types of study outcomes, summary measures across studies could not be calculated. Results are generally presented by estrogen dose, with pills containing $\geq$50 μg of ethinyl estradiol denoted as "high-dose pills," those with <50 and >20 μg as "low-dose pills" and those with ≤20 μg as "very-low-dose pills."

3. Results

3.1. When can a woman start COCs?

Much of the evidence regarding when a woman can start COCs addressed the risk of ovulation based on when, during the menstrual cycle, COCs were initiated. Two studies suggested that 7 days of continuous pill taking is needed to suppress ovulation. The first of these examined ovarian activity among 19 women who had been using different formulations of low-dose pills for at least 3 months [7]. The women had ultrasound examinations on Day 21 (i.e., the last day of pill taking), Day 28 (i.e., the last day of the pill-free interval) and Day 7 of their subsequent pill-taking cycle. All experienced some ovarian follicular activity by Day 28, with 9 having dominant follicles $\geq$7 mm in diameter. By Day 7 of the subsequent cycle, however, the ovaries had returned to the condition seen in the Day 21 scan in all but 1 woman, who had a reduction in follicle diameter. In the second study, 18 women taking low-dose triphasic pills (30-μg ethinyl estadiol/50-μg levonorgestrel, 40-μg ethinyl estradiol/75-μg levonorgestrel, 30-μg ethinyl estradiol/125-μg levonorgestrel) and another 18 women taking low-dose monophasic pills (30-μg ethinyl estradiol/150-μg levonorgestrel) were each divided equally into three groups (6 women per group) after the 7-day pill-free interval: those who took pills for 7 consecutive days only, those who took pills for 14 consecutive days only and those who took pills for 21 consecutive days [8]. One woman in the 7-day group taking the triphasic pill had marked follicular activity with plasma levels of estradiol rising to 1200 pmol/L on the seventh day, with concentrations rising to >2000 pmol/L after she stopped taking pills. Although her serum progesterone levels rose to 6.8 nmol/L by the seventh pill-free day, her FSH and LH levels remained suppressed. No other participant in this study had any evidence of luteinization based on serum FSH, LH or estradiol level.

Two studies examined differences between ovarian activity when COCs were started on Day 1 and when COCs were started on Day 5 [9,10]. In the first study on 14 women using pills containing 30-μg ethinyl estradiol/150-μg levonorgestrel who were randomly assigned to start on Day 1 (n=9) or Day 5 (n=5) of their menstrual cycles, mean serum estradiol levels were significantly higher among the women who started taking COCs on Day 5 rather than on Day 1 [9]. There was no evidence of functioning corpus lutea, based on mid-luteal progesterone levels, in any of the women in either group, and there was no significant difference in the mean serum progesterone levels of these groups. Urinary LH levels were below the mid-cycle peak in all participants, although mean LH levels on Day 16 were significantly higher in the Day 5 group than in the Day 1 group. In the second study, a nonrandomized clinical trial among 22 women using a triphasic formulation (30-μg ethinyl estradiol/50-μg levonorgestrel, 40-μg ethinyl estradiol/75-μg levonorgestrel, 30-μg ethinyl estradiol/125-μg levonorgestrel), 7 of 11 women who started taking the pill on Day 5 of their menstrual cycles developed a dominant follicle $\geq$10 mm in diameter, compared with 1 of 11 women who started on Day 1 [10]. Although mean serum estradiol, FSH and LH levels at the start of pill use were higher in the Day 5 group, none of the women in either group experienced a gonadotropin surge or rise in serum progesterone and the endometrium in all study participants appeared thin on ultrasound examinations.

We identified two studies that examined follicular activity among women who started taking COCs on Day 7

of their cycle [11,12]. The first study randomized 130 women to start COCs (30-μg ethinyl estradiol/300-μg norgestrel) on Day 1 (Group 1), Day 4 (Group 2) or Day 7 (Group 3); used vaginal ultrasonography to measure the participants' maximum follicular diameter on Days 7, 14, 21 and 28; and measured their serum progesterone levels on Days 21 and 28 [11]. The investigators considered that follicle size must generally be >13 mm for ovulation to occur and defined evidence of ovulation as a serum progesterone level >3 ng/mL. The median maximum follicle sizes were 9.0, 9.0 and 13.0 mm for Groups 1, 2 and 3, respectively ($p<.001$). The maximum follicle size exceeded 13 mm for 10.3% of the women in Group 1, 17.2% of those in Group 2 and 44.4% of those in Group 3 ($p=.003$). Serum progesterone measurements indicated that 2 women in Group 1, 1 woman in Group 2 and none in Group 3 had ovulated ($p=.2$). A second study randomized 160 Thai women to start a 20-μg ethinyl estradiol/75-μg gestodene COC on Day 1 or Day 7 [12]. Pelvic sonography was performed on Day 1 and then every other day of the cycle beginning with Day 12 to measure the maximum diameters of dominant follicular-like structures (FLS). In this study, the investigators defined ovulation as "the dominant FLS detected by TVS (transvaginal sonography) and followed-up every other day until its collapse occurred." By this description, 8 of the 78 women in the Day 7 group ovulated compared with none of the 77 women in the Day 1 group ($p=.006$). Maximum follicle sizes and serum hormone levels for women in this study were not reported.

We identified five studies that examined rates of COC continuation and risk for side effects associated with starting COCs on various cycle days [13–17]. Two of these studies examined women who used COCs containing 30-μg ethinyl estradiol/75-μg gestodene and both found shorter duration of menses, fewer episodes of breakthrough bleeding and lower discontinuation rates among women who started on Day 5 than among those who started anytime from Days 1 through 4 [13,14]. The other three studies described the "quick start" method of initiating COC use, in which women with a negative result on a sensitive urine pregnancy test initiate COCs by taking the first pill under the direct observation of their provider at anytime during their menstrual cycle [15–17]. Two of these three studies were observational studies in which either the client or the provider chose the method of initiating various formulations of COCs (quick start or some alternative, such as starting on Sunday). One observational study involved a retrospective assessment of women 22 years or younger who either started COCs using the quick start method ($n=17$) or started on the Sunday after their next menses began ($n=116$). Results of this study showed that 72% of the quick start group continued to use COCs after 3 months, as compared with 56% of the Sunday start group (relative risk [RR], 1.49; 95% confidence interval [CI], 0.97–2.27), but that the continuation rates for the two groups were similar after 12 months (51% for the quick start group and 55% for the Sunday start group; RR, 0.94; 95% CI, 0.68–1.31) [15]. There was no difference between the two groups in risk for side effects including breakthrough bleeding and nausea and vomiting. The second observational study prospectively followed 250 women who had either taken their first pill during the enrollment clinic visit (via the quick start method) or planned to start later that day, the next day, the next Sunday or after having an abortion (via an "alternative start" method) [16]. Of those completing the study, 88% of the 57 women in the quick start group continued to their second pack of pills as compared with 74% of the 169 women in the alternative start group. After adjusting for partner's knowledge of COC use, unhappiness about becoming pregnant in the next 6 months and age, the quick start group was 2.8 times (95% CI, 1.1–7.3) as likely to continue to the second pack of pills as the alternative start group. The only published results of a randomized trial of the quick start method reported on differences in bleeding patterns [17]. Among the 113 women initiating a 35-μg ethinyl estradiol/1-mg norethindrone pill who were randomized to either quick start or starting on the first Sunday after their next menses began and followed for 90 days with bleeding diaries, there was no significant difference in the number of bleeding or spotting days or other bleeding parameters between the two groups.

In summary, we found no direct evidence regarding how the timing of COC initiation during the menstrual cycle affects the risk of pregnancy. Although Level II-1 indirect evidence of fair quality from two small studies suggested that taking hormonally active pills for 7 consecutive days inhibits ovulation, the sample sizes of these studies were small and the results may not have reflected the variability of effect on ovulation in the general population of COC users. In addition, these studies only gave information about ovarian suppression after exactly 7 consecutive days of pill use, although ovarian suppression may have occurred after fewer days of COC use. Level I indirect evidence of fair quality from two studies comparing the effects of starting COCs on Day 5 with those of starting COCs on Day 1 showed that none of the study participants ovulated, although women who started on Day 5 had less suppression of ovarian activity. Level I indirect evidence of fair quality from two other studies that compared the effects of starting COCs on Day 7 with those of starting COCs on Day 1 showed that more follicular activity occurred among those starting on Day 7, with no increase in rates of ovulation for a 30-μg pill but with a significant increase in rates of ovulation for a 20-μg pill. However, the standards for determining whether ovulation occurred varied across studies, with some using fairly low thresholds that may have caused them to overestimate the occurrence of ovulation. Although follicular activity increases as the cycle day on which COCs are initiated increases, it is unclear how this increased activity translates to risk of ovulation and risk of pregnancy. Finally, Levels I and II-1 direct evidence from five fair-quality studies suggests that the day of the cycle on

Table 1
Evidence regarding risk of ovulation after extending the normal 7-day pill-free interval

Reference	Study population	Intervention	Definition of ovulation	Results	Quality
8-day pill-free interval					
Hamilton and Hoogland [26]	30 women aged 20–30 years, new users; the Netherlands	RCT; triphasic 30-μg ethinyl estradiol and 0.5-, 0.75- or 1.00-mg norethindrone; randomized to a complete pill pack ($n=12$), a pill pack with a placebo for Day 7 ($n=9$) or a pill pack with a placebo pill for Day 8 ($n=9$); two consecutive cycles of missed pills	No definition but measured serum progesterone, follicle diameter and cervical mucus	One ovulation, one of nine cycles; 11% (serum progesterone level, 33.4 nmol/L); one woman had luteinized unruptured follicle; cervical mucus unfavorable	I: fair, indirect
Hedon et al. [27]	30 women aged 18–40 years, 1-month users; France	RCT; monophasic 35-μg ethinyl estradiol/250-mg norgestimate; control groups ($n=5$) that did not miss any pill and 16 treatment groups with 5 groups extending the pill-free interval to 8, 9, 10 or 11 (two groups) days; no information about the number of women in each group; one cycle of missed pills	Determined by a classification system of hormonal patterns (same as in Ref. [29])	No ovulation in four cycles	II-1: poor, indirect
9-day pill-free interval					
Killick et al. [28]	28 women, mean age=26.2 years, new users; United Kingdom	RCT; randomized to three COC formulations: (1) monophasic 30-μg ethinyl estradiol/150-μg levonorgestrel; (2) monophasic 30-μg ethinyl estradiol/75-μg gestodene; or (3) triphasic 30-μg ethinyl estradiol/50-μg levonorgestrel, 40-μg ethinyl estradiol/75-μg levonorgestrel, 30-μg ethinyl estradiol/125-μg levonorgestrel; pill-free interval increased from 7 to 9 then 11 days or 11 then 9 days in the second and third of four cycles	No definition but measured serum hormone levels, follicle diameter and cervical mucus scores	No ovulation in 28 cycles; two women had luteinizing hormone surges but no follicle wall rupture (unclear if women were in the 9- or 11 pill-free interval group); cervical mucus Insler scores did not increase	I: fair, indirect
Landgren and Diczfalusy [29]	10 women, mean age=25.9 years, 3-month users; Sweden	Clinical trial; 30-μg ethinyl estradiol/150-μg levonorgestrel; three consecutive cycles of missed pills	Determined by a classification system of hormonal patterns; follicular maturation and luteal function were both normal	No ovulation in 30 cycles; one woman had normal follicular activity but an inadequate rise in luteal activity	II-3: fair, indirect
Hedon et al. [27]	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	No ovulation in four cycles	II-1: poor, indirect
Creinin et al. [24]	69 healthy women aged 18–38 years, 1-month users; USA	RCT; 20-μg ethinyl estradiol/100-μg levonorgestrel ($n=34$) and triphasic 35-μg ethinyl estradiol/180-μg norgestimate; 35-μg ethinyl estradiol/215-μg norgestimate; 35-μg ethinyl estradiol/250-μg norgestimate ($n=35$); one cycle of missed pills	Serum progesterone of ≥3 ng/mL was considered to be presumptive ovulation	Three women in the 20-μg pill group (3/34 cycles; 8.8%) and two in the 35-μg pill group (2/35 cycles; 5.7%) had a ≥3-ng/mL progesterone level, suggesting ovulation, but follicle diameter was <13 mm	I: good, indirect
10-day pill-free interval					
Elomaa et al. [25]	99 women, mean ages=26.3 and 26.8 years, 1-month users; Finland, Netherlands and Belgium	RCT; randomized to three groups: monophasic 20-μg ethinyl estradiol/150-μg desogestrel; monophasic 30-μg ethinyl estradiol/75-μg gestodene; triphasic 30-μg ethinyl estradiol/50-μg gestodene, 40-μg ethinyl estradiol/70-μg gestodene, 30-μg ethinyl estradiol/100-μg gestodene; two cycles of missed pills	Serum progesterone level of ≥9.6 nmol/L	No ovulation in 99 cycles; one woman had luteinized unruptured follicle, 9.6 nmol/L progesterone level (monophasic 30-μg pill)	I: fair, indirect

(*continued on next page*)

Table 1 (*continued*)

Reference	Study population	Intervention	Definition of ovulation	Results	Quality
10-day pill-free interval					
Landgren and Csemiczky [30]	20 women, mean ages=27.4 and 28.1 years, 3-month users; Sweden	RCT; monophasic 30-μg ethinyl estradiol/150-μg desogestrel; triphasic 30-μg ethinyl estradiol/50-μg levonorgestrel, 40-μg ethinyl estradiol/75-μg levonorgestrel, 30-μg ethinyl estradiol/125-μg levonorgestrel; one cycle of missed pills	Determined by a classification system of hormonal patterns (same as in Ref. [29])	Two women ovulated (2/20 cycles; 10%)	II-2: fair, indirect
Hedon et al. [27]	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	No ovulation in four cycles	II-1: poor, indirect
11-day pill-free interval					
Letterie and Chow [31]	15 women, younger than 35 years, new users; Hawaii, USA	RCT; triphasic 35-μg ethinyl estradiol/500-μg norethindrone, 35-μg ethinyl estradiol/750-μg norethindrone, 35-μg ethinyl estradiol/1000-μg norethindrone; three groups missing four consecutive COCs on Days 1–4, 3–6 or 6–9; one cycle of missed pills	Serum progesterone ≥3 ng/mL	No ovulation in five cycles	I: fair, indirect
Killick et al. [28]	Same as in Killick et al.'s 9-day pill-free interval	Same as in Killick et al.'s 9-day pill-free interval	Same as in Killick et al.'s 9-day pill-free interval	Same as in Killick et al.'s 9-day pill-free interval; 28 cycles	I: fair, indirect
Hedon et al. [27]	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	Same as in Hedon et al.'s 8-day pill-free interval	No ovulation in six cycles	II-1: poor, indirect
14-day pill-free interval					
Letterie [32]	10 women aged 25–28 years, new users; Seattle, USA	RCT; two pill regimens: (1) inactive pills Days 1–5, 50-μg ethinyl estradiol/1-mg norethindrone Days 6–10, 0.70-mg norethindrone Days 11–19; inactive pills Days 20–28 for a total pill-free interval of 14 days and (2) inactive pills Days 1–7, 50-μg ethinyl estradiol/0.70-mg norethindrone Days 8–12, 0.70-mg norethindrone Days 13–21, inactive pills Days 22–28 for a total pill-free interval of 14 days; pill-taking regimen restricted to the periovulatory period; two consecutive cycles of missed pills	Serum progesterone ≥6 ng/mL	Six women ovulated in 20 cycles; all occurred during the second cycle	I: fair, indirect

RCT indicates randomized controlled trial.

which women start COCs does not affect their risk for bleeding problems and may increase continuation as compared with more conventional starting strategies.

3.2. What can a woman do if she misses COCs?

Studies assessing the impact of missed pills on women's risk for unintended pregnancy have not been reported; however, several studies have examined ovarian function during the 7-day pill-free interval, during shorter or extended pill-free intervals and during cycles in which pills were deliberately missed on specific days.

Study results have shown that substantial ovarian activity takes place by the end of the normal 7-day pill-free interval. In a study on 19 COC users of various low-dose formulations who underwent ultrasound examinations at three intervals, all women had some follicular development by Day 28 (the last day of the pill-free interval) and follicles ≥7 mm were observed in nine cycles [7]. The investigators considered 7 mm to be the size of a follicle on Day 7 of a normal cycle and concluded that further missed pills would have led to ovulation. Two studies have examined follicle size on Day 7 of the pill-free interval — one among women taking low-dose pills of various formulations [18] and another among women taking either low-dose pills (30-μg ethinyl estradiol/150-μg desogestrel) or very-low-dose pills (20-μg ethinyl estradiol/150-μg desogestrel, 20-μg ethinyl estradiol/75-μg gestodene) [19]. Among the users of the low-dose COCs, between 0% and 27% of cycles had follicles ≥10 mm in diameter, depending on the formulation; for the very-low-dose COC users, between 18% and 50% had follicles ≥10 mm in diameter [18,19]. Another study [20] randomized women to receive one of three COC

formulations (triphasic: 35-μg ethinyl estradiol/180-μg norgestimate, 35-μg ethinyl estradiol/215-μg norgestimate, 35-μg ethinyl estradiol/250-μg norgestimate; monophasic: 30-μg ethinyl estradiol/150-μg desogestrel; monophasic: 20-μg ethinyl estradiol/100-μg levonorgestrel) and examined follicle size every 3 days for three cycles. Overall, 47% of the 36 participants in this study developed follicles ≥10 mm, resulting in 43 dominant follicles. Most of these dominant follicles emerged during the pill-free interval — 86% overall and 86%, 99% and 83% among those women using 35-, 30- and 20-μg ethinyl estradiol pills, respectively. Finally, a study on women using one of three formulations (monophasic: 50-μg ethinyl estradiol/500-μg norgestrel; monophasic: 30-μg ethinyl estradiol/150-μg levonorgestrel; triphasic: varying doses of 30- and 40-μg ethinyl estradiol with 50-, 75- or 125-μg levonorgestrel) suggested that by the end of the 7-day pill-free interval, pituitary function had returned to normal [21]. Although serum FSH, LH and estradiol levels were suppressed at the beginning of the pill-free interval, by the end of the pill-free interval, there was no difference in these levels between COC users and nontreated control subjects in the follicular phase.

We identified two other studies [22,23] that examined whether ovulation takes place when the pill-free interval is extended until a specific follicular size is reached. In the first, a study on low-dose triphasic pill users (30-μg ethinyl estradiol/50-μg levonorgestrel, 40-μg ethinyl estradiol/75-μg levonorgestrel, 30-μg ethinyl estradiol/125-μg levonorgestrel), the pill-free interval was extended until there was a dominant follicle of 12 mm (which took a median of 11 days), at which time COC use was resumed. If the follicle subsequently reached 18 mm, 50,000 U of human chorionic gonadotropin (hCG) was administered to determine whether ovulation would take place in response to this gonadotropin surge. Of 10 women, 8 had follicles that reached 18 mm and were given hCG; ovulation occurred in all 8 of these women [22]. In the second study, in which participants used a very-low-dose monophasic pill (20-μg ethinyl estradiol/75-μg gestodene), the pill-free interval was extended until follicles reached 16 mm in diameter (which took a median of 18 days), at which time participants resumed taking pills and were given 100 μg of buserelin (a gonadotropin-releasing hormone analog) on the third pill-taking day [23]. Ovulation subsequently occurred in four of the five cycles studied.

Because studies have shown that follicular activity resumes during the 7-day pill-free interval, increasing this interval may place a woman at risk of ovulation. In nine studies on low-dose pills in which the pill-free interval was extended to between 8 and 14 days, follicular development and the occurrence of ovulation varied widely (Table 1) [24–32]. In five studies with an extended interval between 8 and 11 days, no ovulation occurred during 208 cycles, as determined through serum hormone measurements and, in some cases, ovarian ultrasound [25,27–29,31]. In the remaining four studies (total $N=84$ cycles), there were 11 presumed ovulations: 1 ovulation occurred among 9 cycles with an 8-day pill-free interval [26], 2 ovulations occurred in 35 cycles with a 9-day pill-free interval [24], 2 ovulations occurred among 20 cycles with a 10-day pill-free interval [30] and 6 ovulations occurred among 20 cycles with a 14-day pill-free interval [32]. In the two studies in which cervical mucus was examined, all women had poor cervical mucus scores throughout the cycle [26,28]. Sample sizes were small in all studies and definitions of ovulation varied or were lacking for several studies.

Evidence suggests that missing pills on days not adjacent to the pill-free interval is not as critical as missing pills on days that are adjacent. We identified nine studies that examined ovarian function when low-dose pills are missed on days not adjacent to the pill-free interval [8,27,31,33–38]. In one of these studies, 54 sterilized women were asked to miss taking low-dose pills (30-μg gestodene/1-mg norethisterone acetate) on 2 consecutive days, anytime between Days 7 and 17 in either the first or the fourth of four cycles; 10 (29%) of 35 women who missed pills during the first cycle and 5 (26%) of 19 women who missed pills in the fourth cycle had an increase in serum progesterone, >4 ng/mL, which was the authors' criterion for escape ovulation [33]. However, the endometrium was suppressed in the 42 women for whom endometrial biopsy tissue was available and the cervical mucus of all 54 participants remained thick and scanty. Another study compared three COCs and the contraceptive patch over five cycles in which Cycles 1, 2, 3 and 5 were normal (21 pill-taking days and 7 pill-free days) but Cycle 4 was only a 10-day cycle (7 pill-taking days and 3 pill-free days) [37]. Results showed the dosing error in Cycle 4 to have no effect on the incidence of ovulation during Cycle 5. In the remaining seven studies that examined the effects of missing pills on days not adjacent to the pill-free interval (a total of 99 cycles), no indication of ovulation was found when pills were missed for up to 4 consecutive days [8,27,31,34–36,38].

We found limited evidence regarding a difference in effect between missing low-dose pills and missing very-low-dose pills. Two studies in which the pill-free interval was extended found more follicular activity among women taking very-low-dose pills than among those taking low-dose pills [24,25]. In one of these, a small study [24] in which women had a 9-day pill-free interval, presumptive ovulation occurred in 3 of 34 cycles among women using a very-low-dose pill (20-μg ethinyl estradiol/100-μg levonorgestrel) and in 2 of 35 cycles among women using a low-dose triphasic pill (35-μg ethinyl estradiol/180-μg norgestimate, 35-μg ethinyl estradiol/215-μg norgestimate, 35-μg ethinyl estradiol/250-μg norgestimate). In the other study [25], in which 99 women were followed for 1 cycle after a 10-day pill-free interval, 40% of women taking a very-low-dose pill (20-μg ethinyl estradiol/150-μg desogestrel) and 24% of women taking one of two low-dose pills (30-μg ethinyl estradiol/75-μg gestodene, 30-μg ethinyl estradiol/50-μg gestodene, 40-μg ethinyl estradiol/70-μg gestodene, 30-μg

ethinyl estradiol/100-μg gestodene) had follicles >18 mm; no ovulation occurred among women in either group.

Three studies on very-low-dose pills compared the effects of a 7-day pill-free interval with those of a shortened or no pill-free interval [39–41]. Two studies found that ovulation was inhibited in most cycles. In one of these, no ovulation occurred in 90 cycles with a 5-day pill-free interval or in 90 cycles with a 7-day pill-free interval among women using 20-μg ethinyl estradiol/75-μg gestodene pills [39]. In the other, no ovulation occurred in 84 cycles with a 4-day pill-free interval and one ovulation occurred in 75 cycles with a 7-day pill-free interval among women taking 15-μg ethinyl estradiol/60-μg gestodene pills [40]. In both studies, LH levels were higher, estradiol levels rose earlier and to a greater degree and more ovarian activity was observed in the 7-day pill-free interval group than among those in the shorter (4 or 5 days) pill-free interval group. The third study randomized 54 women to receive one of three pill formulations: 20-μg ethinyl estradiol/100-μg levonorgestrel for 21 days followed by a 7-day pill-free interval; 20-μg ethinyl estradiol/150-μg desogestrel for 21 days followed by a 2-day pill-free interval followed by 10-μg ethinyl estradiol for 5 days; or 20-μg ethinyl estradiol/150-μg desogestrel for 28 days (i.e., no pill-free interval) [41]. Women with the 7-day pill-free interval experienced less follicular suppression than those with the 2-day pill-free interval followed by 5 days of ethinyl estradiol, who in turn experienced less suppression than women with no pill-free interval. However, variations in the progestin content of the three pills may have accounted for some of the difference in follicular suppression among women undergoing the three regimens.

In summary, we found no direct evidence regarding the effects of missed pills on the risk for pregnancy. Level I indirect studies of fair quality have assessed the risk of ovulation when pills are missed at different times in the menstrual cycle. Studies have shown that follicular activity among COC users resumes during the pill-free interval and, thus, that extending this interval may result in ovulation. Results of studies extending the pill-free interval up to 14 days showed wide variability in the amount of follicular development and in the incidence of ovulation. Among women using low-dose pills, 11 ovulations occurred during a total of 292 cycles (3.8%), with most women who ovulated having abnormal cycles, as indicated by low progesterone levels, thin endometrium and/or poor cervical mucus. The evidence also suggested that missing up to four consecutive pills on days other than those adjacent to the pill-free interval resulted in minimal follicular activity and low risk of ovulation. Studies comparing the effects of missing low-dose pills with those of missing very-low-dose pills suggested more follicular activity among women missing very-low-dose pills, although sample sizes were small. Limitations of this body of evidence include small sample sizes that may not reflect variation in larger populations, lack of a standard definition of ovulation in the studies and difficulty in discerning how ovulation corresponds to the risk of conception.

4. Discussion

An expert working group of 29 family planning experts from 15 countries convened at the WHO in Geneva on April 13–16, 2004, and reviewed the evidence presented in this report. Since the meeting, we identified four additional reports [20,37,38,41] whose results are broadly consistent with those that the expert working group was able to review. The expert working group made recommendations based on the available evidence; where direct evidence was not available, the group relied on indirect evidence and expert opinion [42].

The expert working group recommended that COCs can be started when a clinician is reasonably sure that a woman is not pregnant, preferably within 5 days of the onset of menstrual bleeding, and that no additional contraceptive protection is needed if the method is started within this interval. The preference for starting COCs within 5 days of the onset of menses was based on data suggesting that ovulation suppression was less reliable when COCs were initiated after that time. However, the expert working group also determined that COCs can be started at anytime during the menstrual cycle but recommended that women use additional contraceptive protection for 7 days if they initiate COC use >5 days from the onset of menses, based on data indicating that 7 days of continuous use of hormonally active COCs results in anovulation during that cycle.

In formulating recommendations for missed COCs, the expert working group considered the small risk of ovulation when two or fewer pills are missed. Abstinence or back-up contraception is therefore recommended for 7 days when three or more pills are missed. When three or more pills are missed during the third week of pill taking, the group recommended that a woman should finish the active (hormonal) pills in the current pill pack and then start a new pack the next day, thereby skipping the seven inactive pills in a 28-day pill pack. If two or fewer pills are missed, the woman should take a pill as soon as possible and continue taking pills daily; there is no need for additional contraceptive protection.

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Appendix A. Search Strategies

A.1. When can a woman start COCs?

MEDLINE

1. Contraceptives, oral, combined.mp. or Oral Contraceptive Agent/ (3121)
2. Item 1 and (start: or initiat: or begin: or timing:).tw. (190)
3. Item 2 and (ovar: or ovul: or follic: or estradiol).mp. (122)
4. Item 1 and pill free.tw. (40)
5. Item 1 and patient compliance/ (73)
6. Item 1 and missed pill:.tw. (11)
7. or/ Items 3–6 (228)
8. Item 7 or Quick Start.tw. (238)
9. From Item 8, keep 1–238 (238)

EMBASE

1. Oral contraception/ or exp oral contraceptive agent/ or oral contracept:.tw.
2. Item 1 and (start: or initiat: or begin: or timing).tw.
3. Item 2 and (ovar: or ovul: or follic: or estradiol).mp.
4. Item 1 and pill free.tw.
5. Item 1 and patient compliance/
6. Item 1 and missed pill:.tw.
7. or/ Items 3–6 (612)

A.2. What can a woman do if she misses COCs?

MEDLINE

1. Contraceptives, oral, combined.mp. [mp=ti, ot, ab, nm, hw] (3121)
2. Item 1 and (skip or skipped or miss or missed or forget: or forgot: or pill free or delay or limit or restrict or omit or omission).tw. (123)
3. From Item 2, keep 6 and 8 (2)
4. From Item 2, keep 1–123 (123)

EMBASE

1. Oral contraception/ or exp oral contraceptive agent/ or oral contracept:.tw.
2. Item 1 and (skip or skipped or miss or missed or forget: or forgot: or pill free or delay or limit or restrict or omit or omission).tw. (296)

Appendix B. Study Quality Assessment

B.1. Individual study

Each study was given a rating of Level 1, Level II-1, Level II-2, Level II-3 or Level III based on the study design (Levels of Evidence). Each study was also given a rating of poor, fair or good based on the criteria for grading the internal validity of a study (Criteria for Grading the Internal Validity of Individual Studies). A good study meets all criteria for that study design; a fair study does not meet all criteria but is judged to have no fatal flaw; and a poor study contains a fatal flaw. In addition, the type of evidence was either identified as being direct (the evidence was based on data directly addressing the question) or indirect (the evidence was extrapolated from other relevant data).

B.2. Body of evidence

The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, then the quality of the body of the evidence was lowered by one level.

If the results were consistent, then the quality of the body of the evidence was left at the original level.

Table 1
Levels of evidence

Rating level	Levels of evidence
1	Evidence obtained from at least one properly designed randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group
II-3	Evidence obtained from multiple time series with or without the intervention; dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert communities

Table 2
Criteria for grading the internal validity of individual studies [6]

Study design	Criteria
Systematic reviews	• Comprehensiveness of sources/ search strategy used • Standard appraisal of included studies • Validity of conclusions • Recency and relevance
Case–control studies	• Accurate ascertainment of cases • Nonbiased selection of case patients/control subjects with exclusion criteria applied equally to both • Response rate • Diagnostic testing procedures applied equally to each group • Appropriate attention to potential confounding variables

Randomized controlled trials (RCTs) and cohort studies	• Initial assembly of comparable groups: • For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups • For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts • Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination) • Important differential loss to follow-up or overall high loss to follow-up • Measurements: equal, reliable and valid (includes masking of outcome assessment) • Clear definition of interventions • All important outcomes considered • Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs
Diagnostic accuracy studies	• Screening test relevant, available for primary care, adequately described • Study used a credible reference standard performed regardless of test results • Reference standard interpreted independently of screening test • Handled indeterminate results in a reasonable manner • Spectrum of patients included in study • Sample size • Administration of reliable screening test

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