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Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review☆

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Abstract

Background—Combined hormonal contraceptives (CHCs) are popular methods of reversible contraception in the United States, but adherence remains an issue as reflected in their lower rates of typical use effectiveness. The objective of this systematic review was to evaluate evidence on the effect of missed CHCs on pregnancy rates as well as surrogate measures of contraceptive effectiveness (e.g., ovulation, follicular development, changes in hormone levels, cervical mucus quality).

Study Design—We searched the PubMed database for peer-reviewed articles published in any language from database inception through April 2012. We included studies that examined measures of contraceptive effectiveness during cycles with extended hormone-free intervals or nonadherence (e.g., omission of pills, delayed patch replacement) on days not adjacent to the hormone-free interval. We used standard abstract forms and grading systems to summarize and assess the quality of the evidence.

Results—The search strategy identified 1387 articles, of which 26 met our study selection criteria. There is wide variability in the amount of follicular development and risk of ovulation among women who extended the pill-free interval to 8–14 days; in general, the risk of ovulation was low, and among women who did ovulate, cycles were usually abnormal (i.e., low progesterone levels, small follicles and/or poor cervical mucus) (Level I, good, indirect to Level II-3, fair, indirect). Studies of women who missed one to four consecutive pills or 1–3 consecutive days of delay before patch replacement at times other than adjacent to the hormone-free interval reported little follicular activity and low risk of ovulation (Level I, fair, indirect to Level II-3, poor, indirect). Studies comparing 30 mcg versus 20 mcg mc ethinyl estradiol pills showed more follicular activity when 20 mcg ethinyl estradiol pills were missed (Level I, good, indirect).

Conclusion—Most of the studies in this evidence base relied on surrogate measures of pregnancy risk and ranged in quality. For studies providing indirect evidence on the effects of

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missed CHCs, it is unclear how differences in surrogate measures correspond to pregnancy risk. Fewer studies examined the transdermal patch and vaginal ring than combined oral contraceptives.

Keywords

Combined hormonal contraceptives; Missed pills; Dosing errors; Patient compliance; Contraceptive effectiveness; Pregnancy; Ovarian suppression

1. Introduction

Combined hormonal contraceptives are popular methods of reversible contraception in the United States [1], with near-perfect effectiveness when used consistently and correctly [2]. Adherence remains an issue, however, as reflected in lower rates of typical use effectiveness. For example, 9% of women using combined oral contraceptive pills (COCs), transdermal patch or vaginal ring experience an unintended pregnancy within the first year of use [2].

Nearly half of the 3.1 million unintended pregnancies that occur each year in the United States are attributed to inconsistent or incorrect use of contraception [3]. To help avert unintended pregnancies resulting from patient nonadherence to contraceptive regimens, clinicians and other health care providers often must advise women about what to do after missed contraception, including missed pills, patch replacements and vaginal ring insertions. Nonadherence at different times in the cycle may differentially increase the risk of pregnancy. For example, extending the pill-free interval among COC users may place a woman at increased risk of ovulation since studies have shown that substantial ovarian activity resumes during the 7-day pill-free interval [4–6]. However, missing hormonal contraception on days not adjacent to the hormone-free interval (i.e., midcycle) may not be as likely to result in pregnancy. There may be similar risks for the transdermal patch and vaginal ring given that they have similar properties and mechanisms of action as COCs.

The objective of this systematic review was to evaluate evidence on the effect of missed combined hormonal contraceptives on pregnancy rates as well as surrogate measures of contraceptive effectiveness and ovarian suppression (e.g., follicular development, hormone levels and cervical mucus quality).

2. Methods

We searched the PubMed database for peer-reviewed articles on the effect of missed CHCs or changing the length of the hormone-free interval on pregnancy rates and surrogate measures of contraceptive effectiveness and ovarian suppression (e.g., follicular development, hormone levels and cervical mucus quality) published in any language from database inception through April 2012. We used the following search strategy: ((((((((((“Contraceptives, Oral” [Mesh])) OR (contracepti* AND pill*)) OR (oral AND contracepti*))) OR ((((((contracepti* AND patch)) OR (“Transdermal Patch” [Mesh] AND contracepti*)) OR (“Ortho Evra”[Supplementary Concept])) OR ((contraceptive devices[mesh] OR contraceptive agents[mesh]) AND patch)) OR (orthoevra OR ortho evra))) OR ((((contraceptive devices[mesh] OR contraceptive agents[mesh]) AND ring)) OR

((NuvaRing OR Nuva Ring) OR (vaginal AND ring) OR (contracepti* AND ring))))) AND (“patient compliance” [mesh] OR “drug administration schedule”[mesh] OR “medication adherence”[mesh] OR pill free OR missed pill OR skip OR skipped OR miss OR missed OR forget* OR forgot* OR delay OR limit OR restrict OR omit OR omission OR misuse)) AND (timing OR ovary OR ovary* OR ovul* OR follic* OR estradiol OR pregnan*))) NOT ((((“Contraception, Postcoital”[Mesh])) OR (ulipristal)). Reference lists from articles identified by the search, as well as key review articles, were hand-searched to identify additional articles.

2.1. Selection of studies

We reviewed titles as well as abstracts to identify relevant studies. We included studies that examined measures of contraceptive effectiveness during cycles with extended hormone-free intervals or nonadherence (e.g., omission of pills, delayed patch replacement) on days not adjacent to the hormone-free interval. For COCs, we only included studies of low dose (<50 mcg and >20 mcg ethinyl estradiol) and very low dose (≤20 mcg ethinyl estradiol) preparations. Studies examining continuous use of hormonal contraceptives were excluded, as were abstracts of conference presentations and letters to the editor.

2.2. Assessment of study quality

The evidence was summarized and systematically assessed through the use of standard abstract forms [7]. The quality of each individual piece of evidence (except pharmacokinetic and pharmacodynamic studies) was assessed using the grading system developed by the United States Preventive Services Task Force [8].

2.3. Data synthesis

We present summaries of the evidence in standard evidence tables (Tables 1–4). We did not compute summary measures of association across studies due to diversity of study designs and measurement of outcomes. We did attempt to estimate the total number of ovulations and cycles across similar studies; however, exact numbers were not always presented in the articles, thus estimates represent our best approximations.

3. Results

The search strategy identified 1387 articles, of which 26 met our study selection criteria [9–34]. Of the included articles, 18 examined only COCs [9–23,25,33,34], 1 examined only the transdermal patch [26], 1 examined both COCs and the transdermal patch [24], and 6 examined the vaginal ring [27–32]. Our search strategy did not locate any studies that assessed the impact of missed pills on pregnancy rates. However, we did locate 19 studies that examined ovarian function either during cycles with deliberate extension of the pill-free interval [10–12,14–21,33] or during cycles in which consecutive pills were deliberately missed on days not adjacent to the pill-free interval [9,13–15,21–25,34]. Four of six vaginal ring studies examined the impact of nondeliberate extension of the ring-free interval on pregnancy [27–30]; the other two ring studies assessed the effect of deliberate dosing errors on ovarian function [31,32]. Both studies on the transdermal patch examined the effect of

deliberate dosing errors during weeks not adjacent to the patch-free interval on hormone levels [26] or ovulation [24].

3.1. Combined oral contraceptives

3.1.1. Deliberate extension of the pill-free interval—Ten studies of low- or very low dose pills examined ovarian function during cycles 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) [10,12,14,15,17–21,33]. In five studies with an extended interval between 8 and 11 days, no ovulations occurred during a total of 207 cycles, as determined through serum hormone measurements (e.g., estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone) and, in some cases, ovarian ultrasound [12,15,17,19,21]. In the remaining five studies (total *n*=168 cycles), there were 18 presumed ovulations: one ovulation with an 8-day pill-free interval (total *n*=9 cycles) [14], five ovulations with a 9-day pill-free interval (total *n*=69 cycles) [10], six ovulations with a 10-day pill-free interval (total *n*=70 cycles) [18,33] and six ovulations with a 14-day pill-free interval (total *n*=20 cycles) [20]. Of the 10 studies, sample sizes were small in all but 3 studies [10,12,33], and definitions of ovulation varied (e.g. serum progesterone ≥3 ng/mL, serum progesterone ≥6 ng/mL, collapse of ovarian follicle or presence of folliclelike structure ≥15 mm, and normal follicle maturation with normal luteal secretion) [10,15,18–21,33] or were lacking for several studies [12,14,17]. The largest study included 99 women randomized to one of three treatment groups (i.e., very low dose monophasic desogestrel, low-dose monophasic gestodene or triphasic gestodene COC), all of which included one cycle of extending the pill-free interval to 10 days [12]. No ovulations and one luteinized unruptured follicle were reported in 98 cycles. In two studies with 8-, 9- and 11-day pill-free intervals in which cervical mucus was examined, all women had poor cervical mucus scores throughout the cycles, as determined by a scoring system that considered quantity, spinnbarkeit, clarity, crystallization and leukocytes in one study [14] and mean Insler scores in the other [17].

We identified two other studies that examined whether ovulation took place when the pill-free interval was extended until a specific follicular size was reached [11,16] (Table 1). In the first study of low-dose triphasic pill users, 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, 5000 U of human chorionic gonadotropin (hCG) was administered to determine whether ovulation would take place in response to the gonadotropin surge. Eight of 10 women had follicles that reached 18 mm and were given hCG; ovulation occurred in all eight of these women [16]. In the second study, in which participants used a very low dose monophasic pill, 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 mcg of buserelin (a gonadotropin-releasing hormone analog) on the third pill-taking day [11]. Ovulation subsequently occurred in four out of the five cycles studied.

3.1.2. Deliberate omission of pills on days not adjacent to the pill-free interval —We identified 10 studies that examined ovarian function when low- or very low dose pills were missed on days not adjacent to the pill-free interval (Table 2) [9,13–15,21– 25,34], two

of which observed some evidence of ovulation [9,24]. In one of these two studies, 54 women were asked to miss taking low-dose pills (30 mcg gestodene/1 mg norethindrone acetate) on 2 consecutive days, anytime between days 7 and 17 in either the first or the fourth of four cycles; 10 of 35 (29%) women who missed pills during the first cycle and 5 of 19 (26%) women who missed pills in the fourth cycle had an increase in serum progesterone >4 ng/mL, the authors' criteria for escape ovulation (15 ovulations in 54 cycles) [9]. However, the cervical mucus of all participants remained thick and scanty. The other study compared three different COC formulations 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) [24]. Results showed that, after the dosing error in cycle 4, 12 of 70 (17%) women had presumptive ovulation (i.e., serum progesterone ≥3 ng/mL after disappearance of a large periovulatory follicle observed via ultrasound); however, the rates of ovulation after the dosing error were not different from rates in cycles with correct dosing. The remaining eight studies examined the effects of missing pills on days not adjacent to the pill-free interval (over a total of 132 cycles) and found no indication of ovulation when pills were missed for 1–4 consecutive days [13–15,21–23,25,34]. Definitions of ovulation varied in these studies (e.g. serum progesterone ≥3 ng/mL, serum progesterone >4 ng/mL, normal follicle maturation with normal luteal secretion and disappearance of a large periovulatory follicle observed via ultrasound with serum progesterone ≥3 ng/mL within 7–10 days after follicle disappearance) [9,15,21,24] or were lacking [13,14,22,23,25,34].

3.1.3. Comparison of low-dose and very low dose COCs—We found limited evidence regarding a difference in effect between missing low-dose and very low dose pills. Two studies found more follicular activity among women taking very low dose pills than among those taking low-dose pills after extending the pill-free interval [10,12]. In one of these, a moderate-sized study in which women had a 9-day pill-free interval, presumptive ovulation occurred (i.e., serum progesterone levels were ≥3 ng/mL) in 3 of 34 cycles among women using a very low dose pill (20 mcg ethinyl estradiol/100 mcg levonorgestrel) and in 2 of 35 cycles among women using a low-dose triphasic pill (35 mcg ethinyl estradiol/180 mcg norgestimate; 35 mcg ethinyl estradiol/215 mcg norgestimate; 35 mcg ethinyl estradiol/250 mcg norgestimate) [10]. In the other study, in which 99 women were followed for one cycle after a 10-day pill-free interval, 40% of women taking a very low dose pill (20 mcg ethinyl estradiol/150 mcg desogestrel) and 24% of women taking one of two lowdose pills (30 mcg ethinyl estradiol/75 mcg gestodene; 30 mcg ethinyl estradiol/50 mcg gestodene, 40 mcg ethinyl estradiol/70 mcg gestodene, 30 mcg ethinyl estradiol/100 mcg gestodene) had follicles >18 mm. However, no ovulations (definition not provided) were reported among women in either group [12].

3.1.4. Comparison of COCs containing different progestins—We also found limited evidence regarding a difference in effect between missing COCs containing different progestins. Two studies examined the effect of extending the pill-free interval for up to 11 days on ovarian activity and included COCs with different progestins, both of which found no significant differences in follicular activity, hormone levels or cervical mucus quality [17,18] among formulations containing different progestins.

3.2. Vaginal ring

3.2.1. Nondeliberate extension of the ring-free interval—Four studies reported on pregnancy rates after nondeliberate extension of the ring-free interval [27–30] (Table 3). Of these studies, three were prospective comparative analyses examining pregnancy rates among women with adherent cycles versus nonadherent cycles [27,28,30]. In each of these studies, adherence was defined as ring use not deviating >48 h from the scheduled 21 days times 24 h and the ring-free interval not deviating >24 h from the scheduled 7 days times 24 h, and was measured via self-reported diary cards and/or interactive voice recording systems. Two of these studies reported no pregnancies [27,28]. In the first study, no pregnancies in 635 cycles were reported despite the ring-free interval having been extended >24 h from the scheduled period in 3.5% of cycles (~22 cycles, calculated from manuscript data) [28]. In the second study, conducted among 499 ring users, no pregnancies were reported among nonadherent women despite the ring-free interval having been extended >24 h from the scheduled period in 4.9% of cycles (3.6% of cycles for >24–48 h and 1.3% for >48 h); there was one pregnancy among adherent vaginal ring users [27]. The third prospective comparative analysis, conducted among the largest sample (n=2322) with the longest followup period (i.e., 13 months), reported pregnancies among adherent users and nonadherent users with extended ringfree intervals [30]. Among ~3355 nonadherent cycles (calculated from manuscript data), 11 pregnancies occurred including 1 among a woman who had an 11-day ring-free interval and 1 among a woman who had a 14-day ring-free interval. As the authors reported that 4.8% of 23,298 cycles had extended ring-free intervals, we estimated that 2 pregnancies occurred among 1118 cycles with extended ring-free intervals (~0.18%). Among adherent cycles, 10 pregnancies occurred (10/19,943 cycles, 0.05%). The fourth study was a prospective noncomparative study conducted among 5823 ring users which reported 7 pregnancies (0.12% of users), 2 or 0.03% attributed to extended ring-free intervals (length of extension not stated) [29].

3.2.2. Deliberate dosing errors—Two studies examined the effect on ovarian function after deliberate ring dosing errors [31,32] (Table 3). One prospective noncomparative analysis of data collected from a randomized crossover study included 16 women who deliberately extended the 3-week standard ring use period by 2 weeks to assess the effect on ovarian activity of a simulated forgotten ring removal [32]. All subjects received at least one pretreatment cycle of a COC containing 150 mcg desogestrel and 30 mcg ethinyl estradiol. Failing to remove and replace the ring for up to 2 weeks after standard use did not compromise ovarian suppression, and follicle sizes remained small. In fact, the largest follicular diameters and the highest concentrations of serum estradiol were observed during the first week of ring use, resulting from follicular growth that initiated during the preceding 1-week hormone-free interval. One pharmacodynamic study randomized women into three groups: (a) standard ring use for one cycle followed by use for 21 days with an extended ring-free interval until ovulation for cycle 2 (n=15), (b) standard ring use for one cycle followed by use for 3 days with an extended ring-free interval until ovulation for cycle 2 (n=15) or (c) standard use for one cycle with an extended ring-free interval until a 13-mm follicle was detected by ultrasound, followed by standard use for cycle 2 (n=15) [31]. In this study, median time to ovulation was 19 and 17 days for groups 1 and 2, respectively, with the first ovulation occurring after 13 and 12 days for groups 1 and 2, respectively. In group

3, the median time to develop a 13-mm follicle was 11 days (range 8–21 days), with 50% of women needing an extension of the standard ring-free interval of ≥4 days to achieve this follicle size. Furthermore, ring insertion after the extended ring-free interval in group 3 (until a 13-mm follicle was detected by ultrasound) interfered with ovarian function, as evidenced by decreased serum estradiol levels and disrupted follicle growth.

3.3. Transdermal patch

3.3.1. Deliberate dosing errors during weeks not adjacent to the patch-free interval—Two studies reported on ovulation [24] or hormone levels [26] after deliberate transdermal patch dosing errors during weeks not adjacent to the patch-free interval (Table 4). One randomized controlled trial (RCT) among 52 patch users followed women for three correct dosing cycles followed by a cycle of deliberate dosing errors (cycle 4) [24]. One group wore the patch for 10 consecutive days, and another group wore the patch for 7 days and received no drug on days 8–10. After the dosing errors, mean maximum follicular size between groups did not significantly differ (7.1 versus 6.8 mm, respectively), and rates of ovulation did not differ from rates in cycles 1–3 with correct dosing. One pharmacokinetic study followed 12 women for two patch applications in one cycle [26]. The women first wore the patch for 7 days (proper dosing) and then wore the patch for 10 days (3-day dosing error). Serum hormone levels revealed that mean concentrations of ethinyl estradiol and progestin norelgestromin remained within reference range with the 3-day dosing error.

4. Discussion

We found no direct evidence on the effect of missed pills on the risk for pregnancy; however, we did find indirect evidence that examined ovarian function during cycles in which the pill-free interval was deliberately extended and during cycles in which pills were deliberately missed on days not adjacent to the pill-free week. From this body of evidence, studies of low- or very low dose pills that extended the pill-free interval to 8–14 days found wide variability in the incidence of ovulation and in the amount of follicular development [10,12,14,15,17–21,33]; few women ovulated [10,14,18,20,33], and among women who did ovulate, cycles were usually abnormal (i.e., low progesterone levels, small follicles and/or poor cervical mucus). Evidence from studies included in this systematic review also suggested that missing one to four consecutive pills on days not adjacent to the pill-free interval resulted in little follicular activity and low risk of ovulation [9,13–15,21–25,34]. Although some ovulations were reported, the majority of women who ovulated had poor cervical mucus quality not compatible with sperm penetration. Limited evidence comparing the effects of missing low-dose pills with very low dose pills suggested more follicular activity among women missing very low dose pills, although sample sizes were small [10,12]. Differential effects on follicular activity may be why some currently available guidance on actions to take after missed pills recommends different actions depending on the estrogen content of the COC [35]. Lastly, limited evidence from two studies with small samples comparing the effects of deliberately extending the pill-free interval between pills with different progestins suggested no differences in follicular activity, hormone levels or cervical mucus quality when comparing formulations with levonorgestrel versus those with gestodene or desogestrel [17,18].

Fewer studies on the vaginal ring and transdermal patch were identified. Among vaginal ring users, limited evidence suggests that nondeliberate extension of the ring-free interval >24–48 h from the scheduled period does not increase the risk of pregnancy, although few cycles were classified as having extended ring-free intervals [27,28,30]. Additionally, there is limited evidence from one study to suggest that ring insertion after an extended ring-free interval that allows for follicular development up to 13 mm interrupts ovarian function and further follicular growth [31], and evidence from one study that indicates that inhibition of ovulation is maintained after forgetting to remove the vaginal ring for up to 2 weeks after normal ring use, for a total of 5 continuous weeks of ring use [32]. Among transdermal patch users, there is limited evidence to suggest that missing 1–3 consecutive days before patch replacement (either wearing one patch 3 days longer before replacement or going 3 days without a patch before replacing the next patch) on days not adjacent to the patch-free interval results in little follicular activity and low risk for ovulation [24]. Serum levels of ethinyl estradiol and progestin norelgestromin have also been shown to remain within reference ranges after extending patch wear for 3 days, although these findings are based on one study with 12 women from a single center [26]. There were no studies on extending the patch-free interval.

There are several limitations that make this body of evidence difficult to interpret. Study designs ranged from RCTs to small descriptive studies and pharmacokinetic/pharmacodynamic studies. Sample sizes were generally small (many <30), and therefore, results are unlikely to reflect variations in outcomes of larger populations. These studies used a variety of definitions to assess ovulation, ranging from various cutoffs of serum progesterone levels (e.g., >3 ng/ml, >6 ng/ml, >9.6 nmol/L) to classifications that relied on hormonal parameters and ultrasound measurements; further, some studies classified luteinized unruptured follicles as evidence of ovulation, whereas others did not. Lack of a standard definition of ovulation makes it difficult to compare results across studies. In addition, the timing of measurements taken within the cycle and the number of cycles examined varied across studies. Additionally, all of the studies examining missed COCs (i.e., deliberately extending the pill-free interval or missing pills on days not adjacent to the pill-free interval) reported proxy measures of pregnancy risk. In the absence of studies that examine the effect of missed COCs on pregnancy rates directly, it remains difficult to discern how ovulation corresponds to the risk of pregnancy. For example, although some studies reported that ovulation occurred, many of these also reported that other parameters such as hormone levels and cervical mucus quality were abnormal (i.e., protective against pregnancy). Therefore, the risk of pregnancy may not have actually increased. Although most of the few reports that examined the effect of nondeliberate extension of the hormone-free interval among vaginal ring users provided direct evidence (i.e., reported on pregnancy occurrences), none were specifically designed to examine the effect on pregnancy of varying extended ring-free intervals, making it difficult to draw conclusions. Finally, very few studies examined nonadherence to transdermal patch dosing. Of the two studies that did examine deliberate patch dosing errors during the second patch week, errors beyond 3 days were not explored.

5. Conclusions

In summary, studies on the risk of pregnancy following missed pills, forgotten ring removals and delayed patch replacements have not been published; therefore, we must rely on surrogate measures of pregnancy risk, including ovulation, amount of follicular development and changes in hormone levels. Some studies did report on pregnancy occurrences after nondeliberate extension of ring-free intervals. The body of evidence suggests that there is wide variability in the amount of follicular development and risk of ovulation among women taking low- or very low dose COCs who extend the pill-free interval up to 14 days; in general, the risk of ovulation was low, and among women who did ovulate, cycles were usually abnormal (Level I, good, indirect to Level II-3, fair, indirect). Because follicular activity resumes during the hormone-free interval, extending this interval seems to be a particularly risky time to miss combined hormonal contraception. Studies of women who missed one to four consecutive pills or had 1–3 consecutive days of delay before patch replacement at times other than adjacent to the hormone-free interval reported little follicular activity and low risk of ovulation (Level I, fair, indirect to Level II-3, poor, indirect). Data from one study found that inhibition of ovulation is maintained after 5 weeks of continuous ring use (i.e., forgetting to remove the vaginal ring for up to 2 weeks after 3 weeks of normal ring use) (Level II-3, poor, indirect). Studies comparing 30 mcg ethinyl estradiol pills with 20 mcg ethinyl estradiol pills showed more follicular activity when 20 mcg ethinyl estradiol pills are missed (Level I, good, indirect), and studies comparing the effect of missed combined pills containing levonorgestrel versus those with gestodene or desogestrel found no differences in follicular activity, hormone levels or cervical mucus quality after extending the pill-free interval up to 11 days (Level I, fair, indirect). For studies providing indirect evidence on the effects of missed combined hormonal contraception on surrogate measures of pregnancy (e.g., follicular activity), it is unclear how differences in surrogate measures correspond to pregnancy risk.

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Table 1

Evidence regarding risk of ovulation after deliberate extension of the standard 7-day pill-free interval

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths		Weaknesses		Quality
8-day PFI									
Hamilton and Hoogland, 1989 [14] No source of support stated	30 women aged 20–30 Netherlands, new users	RCT, triphasic 30 mcg EE and 0.5, 0.75, 1.00 mg norethindrone; randomized to a complete pill pack (*n*=12), a pill pack with a placebo for day 1 (*n*=9) or a pill pack with a placebo pill for day 2 (*n*=9); 1 cycle of missed pills	No definition	1 ovulation in 9 cycles (11%) (serum progesterone level 33.4 nmol/L); 1 women with luteinized unruptured follicle. Cervical mucus unfavorable	-	Women had history of regular cycles	- Small sample - No definition of ovulation - Randomization procedures not described - Single center		I, fair, indirect
Hedon et al., 1992 [15] No source of support stated	47 women, age 18–40 years, France, mix of new and previous users	RCT; 35 mcg EE/250 mg norgestimate; control group (*n*=5) which did not miss any pills and 16 treatment groups with 5 groups extending the PFI to 8 (*n*=4), 9 (*n*=4), 10 (*n*=4) or 11 (*n*=6); 1 cycle of missed pills	Normal follicular maturation and normal luteal secretion	No ovulations in 4 cycles	- -	Women had history of regular cycles Definition of ovulation	- Small sample - Randomization procedures not described - Some women participated in more than one study group - Single center		I, poor, indirect
9-day PFI									
Landgren and Diczfalusy, 1984 [19] WHO (HRP)	10 women, mean age 25.9, Sweden, users for ≥3 months	Descriptive study; 30 mcg EE/150 mcg LNG; 3 consecutive cycles of missed pills	Normal follicular maturation and normal luteal secretion	No ovulations in 30 cycles; one woman had normal follicular activity but an inadequate rise in luteal activity	- -	Women had history of regular cycles Definition of ovulation	- Small sample		II-3, fair, indirect
Killick et al., 1990 [17] Schering Laboratories	28 women, mean age 26.2, United Kingdom, new users	RCT; randomized to 3 COC formulations: (a) monophasic 30 mcg EE/150 mcg LNG, (b) monophasic 30 mcg EE/75 mcg gestodene or (c) triphasic 30 mcg EE/50 mcg LNG, 40	No definition but measured serum hormone levels, follicle diameter, cervical mucus scores	No ovulations in 28 cycles; 2 women with LH surges but no follicle wall	-	Women had history of regular cycles	- Small sample - No definition of ovulation		I, fair, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
		mcg EE/75m mcg LNG, 30 mcg EE/125 mcg LNG. PFI increased from 7 to 9 then 11 days, or 11 then 9 days, in 2nd and 3rd of 4 cycles		reported (based on women were in the 9 to 11 PFI group) Mean cervical mucus Insler scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between COC formulations		- Randomization procedures not described - Single center	
Hedon et al., 1992 [15] No source of support stated	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	No ovulations in 4 cycles	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	I, poor, indirect
Creinin et al., 2002 [10] Ortho-McNeil Pharmaceutical Corporation	69 healthy women, 18–38 years, USA, 1-month users	RCT; 20 mcg EE/100 mcg LNG (*n*=34) and triphasic 35 mcg EE/180 mcg norgestimate; 35 mcg EE/215 35 mcg norgestimate; EE/250 mcg norgestimate (*n*=35); 1 cycle of missed pills	Serum progesterone ≥3 ng/mL	3 women in the 20 mcg pill group (3/34 cycles; 8.8%) and 2 women in the 35 mcg pill group (2/35 cycles; 5.7%) had presumptive ovulation, but follicle diameter <13 mm.	- Women had history of regular cycles - Moderate sample - Definition of ovulation - Randomization procedures described - Multiple centers		I, good, indirect
10-day PFI							
Landgren and Csemiczky, 1991 [18] Organon AB	20 women, mean ages 27.4 and 28.1, Sweden, users for ≥3 months	RCT; 2 COC groups: (a) monophasic 30 mcg EE/150 mcg desogestrel; (b) triphasic 30 mcg EE/50 mcg LNG, 40 mcg EE/75 mcg LNG, 30 mcg EE/125 mcg LNG; 1 cycle of missed pills	Same as Landgren and Diczfalusy, 1984, 9-day PFI	2 women ovulated (2/20 cycles, 10%), one in each COC group No significant	- Women had history of regular cycles - Definition of ovulation	- Small sample - Randomization procedures not described - Single center	I, fair, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
				differences in follicular growth or serum hormone levels between COC groups. differences in follicular growth or serum hormone levels between COC groups. differences in follicular growth or serum hormone levels between COC groups. differences in follicular growth or serum hormone levels between COC groups. differences in follicular growth or serum hormone levels between COC groups. differences in follicular growth or serum hormone levels between COC groups.			
Hedon et al., 1992 [15] No source of support stated	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	No ovulations 4 cycles	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	I, poor, indirect
Elomaa et al., 1998 [12] Wyeth-Ayerst International Inc.	99 women, mean age 26, Finland, Netherlands and Belgium, 1-month users	RCT; randomized to 3 groups: monophasic 20 mcg EE/150 mcg desogestrel; monophasic 30 mcg EE/75 mcg gestodene; triphasic 30 mcg EE/50 mcg gestodene, 40 mcg EE/70 mcg gestodene, 30 mcg EE/100 mcg gestodene; 1 cycle of missed pills	No definition	No ovulations in 98 cycles; 1 woman taking monophasic 30 mcg pill with LUF (9.6 nmol/L progesterone level)	- Women had history of regular cycles - Moderate sample - Randomization procedures described - Multiple centers	- No definition of ovulation	I, good, indirect
Klipping et al., 2008 [33] Bayer Schering Pharma	105 women (50 in group of interest), ages 18–35, Netherlands	RCT, 2 groups followed for 3 cycles: 20 mcg EE/3 mg drospirenone either with 7- or 4-day PFI increased to 10 or 7 days in 3rd cycle; ovarian ultrasound, estradiol, LH, FSH and progesterone were measured	Collapse of ovarian follicle or presence of follicle-like structure ≥15 mm	4 women ovulated in 21/7 group (4/50 cycles, 8%)	- Moderate sample of those in 21/7 group - Definition of ovulation - Randomization procedures described	- Unclear if women had history of regular cycles - Single center	I, fair, indirect
11-day PFI							
Killick et al., 1990 [17] Schering Laboratories	Same as Killick et al., 1990 [17], 9-day PFI	Same as Killick et al., 1990 [17], 9-day PFI	Same as Killick et al., 1990 [17], 9-day PFI	No ovulations in 28 cycles; 2 women with LH surges but no follicle wall rupture (unclear if women were in the 9 or 11 PFI group). Mean cervical mucus Insler	Same as Killick et al., 1990 [17], 9-day PFI	Same as Killick et al., 1990 [17], 9-day PFI	I, fair, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
					scores did not increase. No significant differences in follicular activity, hormone levels or cervical mucus quality between		
Hedon et al., 1992 [15] No source of support stated	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	No ovulations in 6 cycles	Same as Hedon et al., 1992 [15], 8-day PFI	Same as Hedon et al., 1992 [15], 8-day PFI	I, poor, indirect
Letterie and Chow, 1992 [21] No source of support stated	15 women, aged less than 35, USA, new users	RCT; triphasic 35 mcg EE/500 mcg norethindrone, 35 mcg EE/750 mcg norethindrone, 35 mcg EE/ 1000 mcg norethindrone; 3 groups (1 described here): missing 4 consecutive COCs on days 1–4 (*n*=5); 1 cycle of missed pills	Serum progesterone ≥3 ng/mL	No ovulations in 5 cycles	- Women had history of regular cycles. - Definition of ovulation - Randomization procedures described	- Small sample - Single center	I, fair, indirect
14-day PFI							
Letterie, 1998 [20] No source of support stated	10 women, age 25 to 28 years, USA, new users	RCT; 2 pill regimens: (a) inactive pills days 1–5, 50 mcg EE/1 mg norethindrone days 6–10, 0.70 mg norethindrone days 11–19; inactive pills days 20–28 for a total PFI of 14 days; (b) inactive pills days 1–7, 50 mcg EE/0.70 mg norethindrone days 8–12, 0.70 mg norethindrone days 13–21, inactive pills days 22–28 for a total PFI of 14 days; pill-taking regimen restricted to the periovulatory period; 2 consecutive cycles of missed pills	Serum progesterone ≥6 ng/mL	6 women ovulated in 20 cycles; all occurred during the 2nd cycle	- Women had history of regular cycles - Definition of ovulation	- Small sample - Randomization procedures not described - Single center	I, fair, indirect
PFI extended until a specific follicular size is achieved							

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
Killick, 1989 [16] No source of support stated	10 women, ages not given, UK, current users for at least 3 months	Descriptive study; triphasic 30 mcg EE/50 mcg LNG for 6 days, 40 mcg EE/75 mcg LNG for 5 days, 30 mcg EE/125 mcg LNG for 10 days; daily pelvic ultrasonography starting with PFI and continuing until dominant follicle of 12 mm seen; on that day, women resumed COCs; when dominant follicle of 18 mm was seen, 5000 U of hCG was administered; daily monitoring continued until dominant follicle disappeared	No definition	12-mm follicles developed between 7 and 16 days (median of 11 days); 2 women never had follicle of 16 mm and were not given hCG; other 8 women received hCG and experienced follicle wall rupture within 48 h; serum EE and progesterone values were within the range of normal ovulatory cycles		- Small sample - No definition of ovulation	II-3, poor, indirect
Elomaa and Lahteenmaki, 1999 [11] Wyeth Medica Ireland	5 women, 18–30 years, Finland	Descriptive study; 20 mcg EE/75 mcg gestodene; after 21 days of pill taking, the PFI continued until 16-mm follicle was achieved, at which time the woman resumed taking COCs; 100 mcg of GnRH analog (buserelin) was administered on the third day of pill taking; daily monitoring continued until dominant follicle disappeared	Significant LH increase defined as 30% increase in mean concentration of 3 consecutive LH samples in midfollicular phase	4 of 5 women ovulated; 1 had unruptured follicle; 16-mm follicle developed between 14 and 26 days after stopping COCs, median 18 days	- Women had history of regular cycles - Definition of ovulation	- Small sample	II-3, fair, indirect

Abbreviations: EE=ethinyl estradiol; GnRH=gonadotropin-releasing hormone; FSH=follicle-stimulating hormone; LH=luteinizing hormone; LNG=levonorgestrel; PFI=pill-free interval; WHO=World Health Organization.

Table 2

Evidence regarding risk of ovulation after pills deliberately missed on days not adjacent to the PFI

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
Morris et al., 1979 [22] Schering Chemicals Ltd	10 women, ages 20–40, England, current COC users	Nonrandomized controlled trial; 30 mcg EE/150 mcg LNG; subjects were instructed to omit their day 4 pill (*n*=7) or their day 19 pill (*n*=3); plasma estradiol, progesterone, FSH, LH, LNG, cervical mucus measured	No definition	No ovulations in 10 cycles. Cervical mucus specimens remained thick in all participants, and hormone levels remained suppressed		- Small sample - No definition of ovulation - Unclear if women had history of regular cycles	II-1, poor, indirect
Chowdhury et al., 1980 [9] Source of support not stated	64 women [54 in study groups (sterilized) and 10 in control group], ages 18–35, India	Nonrandomized controlled trial; 30 mcg EE/1 mg norethindrone acetate; subjects asked to miss 2 consecutive COC pills between day 7 and 17 in the 1st or 4th treatment cycle; 10 women did not miss any pills; serum progesterone, lateral vaginal wall smears, cervical mucus samples and endometrial biopsy measured	Serum progesterone >4 ng/mL	Control group: 1 woman with ovulation in 10 cycles Study groups: 10/35 in first treatment cycle and 5/19 in fourth treatment cycle ovulated (15 ovulations in 54 cycles); however, cervical mucus quality was poor throughout the cycles based on quantity, nature, clarity, ferning and spinnbarkeit	- Women had history of regular cycles - Moderate sample - Definition of ovulation	- Comparability of groups unknown	II-1, fair, indirect
Nuttall et al., 1982 [23] Schering Chemicals Ltd	6 women, ages 18–40, England, new users	Descriptive study; 20 mcg EE//250 mcg LNG; subjects were followed for 4 cycles; in 2nd cycle, subjects missed pill 10 (day 14); in 3rd cycle, subjects missed pills 9 and 10 (days 13 and 14); plasma	No definition	No ovulations in 12 cycles	- Women had history of regular cycles	- Small sample - No definition of ovulation	II-3, poor, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
		estradiol, progesterone, LH, FSH and cervical mucus measured estradiol, progesterone, LH, FSH and cervical mucus measured estradiol, progesterone, LH, FSH and cervical mucus measured					
Wang et al., 1982 [34] Schering; WHO	32 women, mean age 23.8 years, Sweden, current users	RCT; 30 mcg EE/150 mcg LNG; subjects were randomized to miss 2 consecutive COC pills on days 9–10, 11–12, 14–15 or 17–18 (*n*=8 in each group); serum estradiol, progesterone, norgestrel, LH, FSH, SHBG and bleeding patterns measured	No definition	Progesterone levels >1.5 nmol/l in 1/32 women; this participant had not complied with study regimen and did not start taking pills until day 10; no evidence of ovulation in other participants (31 cycles)	- Women had history of regular cycles	- Small sample - No definition of ovulation - Randomization procedures not described - Single center	I, fair, indirect
Smith et al., 1986 [25] Schering Chemicals Ltd	36 women, ages 20–36 years, Scotland, 1-month users	Nonrandomized controlled trial: women taking triphasic [30 mcg EE/50 mcg LNG, 40 mcg EE/75 mcg LNG, 30 mcg EE/125 mcg LNG (*n*=18)] or monophasic [30 mcg EE/150 LNG (*n*=18)] COCs; divided into 3 groups after 7-day PFI; Group 1: pill-taking for 7 days only (*n*=12); Group 2: pill-taking for 14 days only (*n*=12); Group 3: pill-taking for 21 days (*n*=12) (correct dosing); plasma estradiol, progesterone, LH and FSH measured	No definition	No ovulations in 24 cycles. One woman in group 1 (incorrect dosing) demonstrated marked follicular activity, but no LH surge was detected, and estradiol levels were abnormal	- Groups appear comparable related to age and weight. - Multiple centers	- Small sample - No definition of ovulation - Unclear if women had history of regular cycles	II-1, fair, indirect
Hamilton and Hoogland, 1989 [14] No source of support stated	30 women aged 20–30, Netherlands, new users	RCT, triphasic 30 mcg EE and 0.5, 0.75, 1.00 mg norethindrone; randomized to a complete pill pack (*n*=12), a pill pack with a placebo for day 1 (*n*=9) or a pill pack with a placebo pill for day 2 (*n*=9); 1 cycle of missed pills	No definition	No ovulations in 9 cycles	- Women had history of regular cycles	- Small sample - No definition of ovulation - Randomization procedures not described - Single center	I, fair, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
Hedon et al., 1992 [15] No source of support stated	47 women, age 18–40 years, France, mix of new and previous users	Nonrandomized controlled trial; 35 mcg EE/250 mg norgestimate; control group (*n*=5) which did not miss any pills and 16 treatment groups with 11 groups omitting 1–4 consecutive pills beginning on days 6 or 12 (*n*=14), or omitting 1–3 consecutive pills beginning on day 18 (*n*=10); 1 cycle of missed pills	Normal follicular maturation and normal luteal secretion	No ovulations in 24 cycles	- Women had history of regular cycles - Definition of ovulation	- Small sample - Randomization procedures not described - Some women participated in more han one study group - Single center	I, poor, indirect
Letterie and Chow, 1992 [21] No source of support stated	15 women, aged less than 35, USA, new users	RCT; triphasic 35 mcg EE/500 mcg norethindrone, 35 mcg EE/750 mcg norethindrone, 35 mcg EE/1000 mcg norethindrone; 3 groups (2 described here): missing 4 consecutive COCs on days 3–6 (*n*=5), or 6–9 (*n*=5); 1 cycle of missed pills	Serum progesterone ≥3 ng/mL	No ovulations in 10 cycles	- Women had history of regular cycles - Definition of ovulation - Randomization procedures described	- Small sample - Single center	I, fair, indirect
Pierson et al., 2003 [24] Johnson & Johnson Pharmaceutical Research and Development LLC	124 women (COC group *n*=72), 18–35 years, USA and Canada	RCT, 5 groups (3 described here): (a) triphasic COC (30 mcg EE/50 mcg LNG, 40 mcg EE/75 mcg LNG, 30 mcg EE/125 mcg LNG); (b) monophasic COC (20 mcg EE/100 mcg LNG); (c) triphasic COC (35 mcg EE/180 mcg norgestimate, 35 mcg EE/215 mcg norgestimate, 35 mcg EE/250 mcg norgestimate). Correct dosing in cycles 1, 2, 3, 5. Dosing error in cycle 4, a 10-day cycle: all 3 COC groups had correct dosing on days 1–7 and received no drug on days 8–10. Ovarian ultrasound performed prestudy and during cycles 1–5. Blood serum levels of EE, LH, FSH and progesterone measured	Disappearance of a large periovulatory follicle observed via ultrasound and progesterone levels ≥3 ng/mL within 7–10 days after follicle disappearance	12 ovulations in 70 cycles (17%) in cycle 5 (after dosing error); Group 1: 4/21 (19%); Group 2: 5/25 (20%); Group 3: 3/24 (13%). Rates of ovulation in cycle 5 (after dosing error) were not different from rates in cycles 1–3 (with correct dosing)	- Women had history of regular cycles - Moderate COC sample - Definition of ovulation - Multiple centers	- Randomization procedures not described	I, fair, indirect
Endrikat et al., 2004 [13] Schering AG, Berlin	6 women, ages 24–26, Germany	Nonrandomized controlled trial; 30 mcg EE/75 mcg gestodene; 1 untreated cycle and 3 cycles of treatment; cycle 1: 21 days of pills and	No definition	No ovulations in 12 cycles		- Small sample - No definition of ovulation	II-1, poor, indirect

Reference, sources of support	Study population	Study design/intervention	Definition of ovulation	Results	Strengths	Weaknesses	Quality
		7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups 7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups 7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups 7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups 7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups 7-day PFI; cycle 2: 3 women skipped pills on days 6 and 7 and 3 women skipped pills on days 11 and 12; cycle 3: same skip pattern but in alternate groups				– Comparability of groups unknown – Unclear if women had history of regular cycles	

Abbreviations: SHBG=sex hormone binding globulin; WHO=World Health Organization.

Table 3

Evidence regarding risk of pregnancy or ovulation after vaginal ring dosing errors

Reference, sources of support	Study population	Study design/intervention	Definition of adherence/ dosing error	Outcome	Results	Strengths	Weaknesses	Quality
Nondeliberate extension of the RFI								
Bjarnadottir et al., 2002 [28]	121 women using NuvaRing for 635 cycles, ages 18–40, multiple centers in 5 European countries	Prospective comparative analysis (adherent versus nonadherent cycles) of data from 1 RCT and 2 nonrandomized trials; NuvaRing users followed for 6 cycles of standard use[a] ; FU after cycles 3 and 6 or at premature discontinuation	- Period of ring use did not deviate >48 h from scheduled 21 days × 24 h, and RFI did not deviate >24 h from the scheduled 7 days × 24 h	Pregnancy: tested via urine if pregnancy suspected during study and via serum test for β-hCG at end of study	No pregnancies in 635 cycles reported despite RFI extended >24 h from scheduled period in 3.5% of cycles (~22)	- Large sample - Pregnancy measurement described - Adherence tracked on diary cards - Multiple centers	- Unclear if women had regular cycles - Details on length of extended RFI not reported nor # of cycles with other types of dosing errors	II-2, poor, direct
Dieben et al., 2002 [30] (Some data also reported in Roumen et al., 2001 [36] and Roumen et al., 2002 [37]) NV Organon	2322 women using NuvaRing for 23, 298 cycles, mean age 28.2, multiple centers in Europe, Canada, USA	Prospective comparative analysis (adherent versus nonadherent cycles) of data collected from 2 noncomparative studies; NuvaRing users followed for 13 cycles; FU occurred during 1st week after cycles 3, 6, 9 and 13 months postinitiation of standard use[a]	- Same as above - Shortened RFIs imply duration <6 days; extended RFIs imply duration >8 days	Same as Bjarnadottir et al., 2002 [28]	14.4% of users (~3355 cycles) were nonadherent; 4.8% of users (~1118 cycles) had extended RFI; 11 pregnancies among nonadherent women (11/3355 cycles, 0.33%): 1 had 11-day RFI, 1 had 14-day RFI, 9 had 2+ consecutive days without ring use during ring-use period or misunderstood proper use. 10 pregnancies among adherent women (10/19,943 cycles, 0.05%)	- Large sample - Adherence tracked on diary cards and interactive voice recording systems - Multiple centers	- Unclear if women had regular cycles - Pregnancy rates not reported separately for different types of dosing errors (unable to calculate since # of cycles with different dosing errors not known)	II-2, poor, direct
Ahrendt et al., 2006 [27] Oragon	499 women, mean age 26.6, multiple centers in 10 European countries	Prospective comparative analysis (adherent versus nonadherent cycles) of data collected from 1 RCT; NuvaRing users followed for 13 cycles of standard use[a]	Same as Bjarnadottir et al., 2002 [28]	Same as Bjarnadottir et al., 2002 [28]	No pregnancies reported among nonadherent women despite RFI extended >24 h from scheduled period in 4.9% of cycles (3.6% of cycles for >24–48 h and 1.3% for >48 h); 1 pregnancy reported among adherent women.	- Large sample - Pregnancy measurement described - Adherence tracked on diary cards - Multiple centers	- Unclear if women had regular cycles - Details on # of adherent and nonadherent cycles not provided	II-2, poor direct

Reference, sources of support	Study population	Study design/intervention	Definition of adherence/ dosing error	Outcome	Results	Strengths	Weaknesses	Quality
Brucker et al., 2008 [29] Organon	5823 women using NuvaRing, median age 29.4, Germany	Prospective noncomparative study; FU visits at 3, 6 months postinitiation of standard use[a]	- Definition of adherence not stated	Pregnancy — method of measurement not stated	7 pregnancies (0.12% of users); 3 due to nonadherence [extended RFI in 2 and interruption of ring use (timing and duration not known) in 1]; 1 due to repeated ring expulsion or loss; 3 unknown	- Large sample	- Unclear if women had regular cycles - No definition of adherence - Adherence not systematically tracked - Pregnancy measurement not described - Limited information on nonadherence - Single center	II-3, poor, direct
Deliberate dosing errors								
Mulders and Dieben, 2001 [32] NV Organon	16 women, ages 18–35 years, 1 center, Netherlands	Prospective noncomparative analysis of data collected from randomized crossover study; NuvaRing use for 3 weeks extended by additional 2 weeks, 2 groups, NuvaRing use was either pre- or proceeded by 1 cycle of 30 mcg EE/150 mcg desogestrel (n=8 for each group). Ovarian ultrasound, LH, FSH, estradiol and progesterone measured	- Standard use[a] - Extended ring use for additional 2 weeks simulates forgotten ring removal	Ovulation — definition not stated	- No ovulations in 16 cycles with dosing errors - Follicular size remained small during the extended period of ring use - Largest follicular diameters and highest concentrations of estradiol were during 1st week of ring use	- Adherence tracked on diary cards	- Unclear if women had regular cycles - Small sample - No definition of ovulation	II-3, poor, indirect
Mulders et al., 2002 [31] NV Organon	51 women, ages 18–35 years, 1 center, Netherlands	PD study with 3-group randomization: (a) NuvaRing standard use[a] for cycle 1, use for 21-days with extended RFI until ovulation for cycle 2 (n=15); (b) NuvaRing standard use[a] for cycle 1, use for 3 days with extended RFI until ovulation for cycle 2 (n=15); (c) NuvaRing use for 21 days with extended RFI until 13-mm follicle detected by ultrasound, followed by standard use[a] for cycle 2 (n=15),	- Criteria not provided, but adherence was determined by number of hours of ring use per day	Ovulation — definition not stated	Median time to ovulation was 19 (Group 1) and 17 (Group 2) days after ring removal (cycle 2), with 1st ovulation after 13 (Group 1) and 12 (Group 2) days; median time to develop 13-mm follicle (cycle 1) for Group 3 was 11 days (range 8–21 days); 50% of women needed extension of RFI ≥4 days. Ring insertion after extended RFI for Group 3 interfered with ovarian function	- Moderate sample - Adherence tracked on diary cards - Randomization procedures described	- Unclear if women had regular cycles - Criteria for adherence not provided - No definition of ovulation - Single center	*b*

Abbreviations: FU=follow-up; PD=pharmacodynamic.

[a] Standard use for vaginal ring defined as 21 days of ring use followed by 7-day ring-free interval.

[b] Quality of pharmacodynamic studies not assessed.

Table 4

Evidence regarding risk of ovulation after deliberate dosing errors during weeks not adjacent to the patch-free interval

Reference, sources of support	Study population	Study design/intervention	Outcome	Results	Strengths		Weaknesses		Quality
Abrams et al., 2001 [26] RW Johnson Pharmaceutical Research Institute	12 women, ages 18–44, 1 center, USA	PK study, patch users followed for 2 patch applications: the 1st for 7 days (proper dosing) and the 2nd for 10 days (3-day dosing error); serum levels of EE and progestin norelgestromin drawn prior to patch application, and at specific times on days 1–3 and 6–19	Serum levels of EE and progestin norelgestromin	Mean serum concentrations of EE and progestin norelgestromin remained within reference ranges (25–75 pg/mL and 0.6–1.2 ng/mL, respectively) during 7-day patch wear period and when patch deliberately worn for 10 days 3-day dosing error).	- Women had history of regular cycles - All patches adhered during study period		- Small sample - Single center		*a*
Pierson et al., 2003 [24] Johnson & Johnson Pharmaceutical Research & Development, LLC	124 women (patch group *n*=52), ages 18–35 years, 12 centers, USA and Canada	RCT, 5 groups (2 described here). Correct dosing in cycles 1, 2, 3 and 5. Dosing error in cycle 4, a 10-day cycle: patch group 1 wore one patch for 10 consecutive days; patch group 2 had correct dosing on days 1–7 and received no drug on days 8–10. Ovarian ultrasound performed prestudy and during cycles 1–5. Blood serum levels of EE, LH, FSH and progesterone measured	Ovulation: disappearance of a large periovulatory follicle observed via ultrasound and progesterone levels ≥3 ng/mL within 7–10 days after follicle disappearance	After dosing errors (cycle 5), mean maximum follicular size between groups 1 and 2 did not significantly differ (7.1 mm versus 6.8 mm, respectively). Ovulation for patch groups combined (data not reported for each group separately) for cycles 1, 2 and 3 (correct dosing) were 0/49 (0%), 1/48 (2%) and 0/48 (0%), respectively. Ovulation was 1/43 (2%) after dosing errors (cycle 5)	- Women had history of regular cycles - Moderate sample of patch users - Definition of ovulation - Multiple centers		- Randomization procedures not described		I, fair, indirect

Abbreviation: PK=pharmacokinetic study.

[a] Quality of pharmacokinetic studies not assessed.