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► To cite this version:

Nathalie Chabbert-Buffet, Christian Jamin, Inaki Lete, Paloma Lobo, Rossella E. Nappi, et al.. Missed pills: frequency, reasons, consequences and solutions. *European Journal of Contraception and Reproductive Health Care*, 2017, 22 (3), pp.165-169. 10.1080/13625187.2017.1295437 . hal-01560167

HAL Id: hal-01560167

<https://hal.sorbonne-universite.fr/hal-01560167>

Submitted on 17 Jul 2017

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1 Missed pills: frequency, reasons, consequences and solutions

2

3 Nathalie Chabbert-Buffet[#], Christian Jamin[‡], Iñaki Lete^{*}, Paloma Lobo[§], Rossella E. Nappi[^],
4 Axelle Pintiaux[§], Günther Häusler^{**} and Christian Fiala[†]

5 [#] Department of Obstetrics and Gynaecology, APHP Tenon Hospital, Pierre and Marie Curie
6 University, Paris, France; [‡]169, boulevard Haussmann, Paris, France; ^{*}Department of
7 Obstetrics and Gynaecology, Araba University Hospital, Vitoria-Gasteiz, Spain; [§]Department
8 of Obstetrics and Gynaecology, Infanta Sofía University Hospital, San Sebastián de los
9 Reyes, Madrid, Spain; [^]Research Centre for Reproductive Medicine, Gynaecological

10 Endocrinology and Menopause, IRCCS San Matteo Foundation, Department of Clinical,
11 Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy; [§]Department of
12 Obstetrics and Gynaecology, Citadelle Hospital, Liège University, Liège, Belgium;

13 ^{**}Department of Gynaecology and Gynaecological Oncology, AKH-Wien, Vienna, Austria;
14 and [†]Gynmed Ambulatorium, Vienna, Austria, and Department of Women's and Children's
15 Health, Karolinska Institutet, Stockholm Sweden.

16 Correspondence: Nathalie Chabbert-Buffet, Department of Obstetrics and Gynaecology,
17 APHP Tenon Hospital, Pierre and Marie Curie University, 75020 Paris, France. Tel: +33 56
18 01 77 48. Fax: +33 1 56 01 67 15. E-mail: nathalie.chabbert-buffet@aphp.fr

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ABSTRACT

Oral hormonal contraception is an effective contraceptive method as long as a regular daily intake is maintained. However, this routine is a constraint for many women and can lead to missed doses, pill discontinuation and/or unintended pregnancy. Risk factors for missed pills include user characteristics, cultural aspects, a lack of information about the choice of contraceptive options and a lack of involvement in the decision. The formulation of the combined oral contraceptive, including the type of dosing regimen (21-day or 28-day packs), can also negatively influence efficacy and compliance. As ovarian activity is not fully suppressed, the risk of failure is greatest when the hormone-free interval (HFI) is prolonged. Continuous pill intake or long-cycle regimens can reduce the risks of follicular development and thus the likelihood of ovulation and unintended pregnancy. A shortened or eliminated HFI and a progestin with a longer half-life (providing better suppression of ovarian activity) may be an option to reduce the negative consequences of missed pills in oral contraception.

KEYWORDS

Compliance; Efficacy; Half-life; Hormone-free interval; Missed pill; Nomegestrol acetate; Non-compliance; Progestin; Regimen.

1 INTRODUCTION

2

3 Fertility has been a concern for people throughout history. Pre-20th Century contraceptive
4 methods included male condoms and coitus interruptus, and with the development of
5 combined oral contraceptives (COCs) in the 1960s women gained more control¹. However,
6 the high contraceptive efficacy of COCs depends on regular daily intake^{2,3} and compliance
7 problems are common among all age groups⁴. Efforts were made to improve compliance
8 (including easy use, minimal side effects and better tolerability), but with poor results³.

9

10 In this narrative review we will summarize available data from the literature on missed pill
11 occurrence and its consequences, as well as discuss available solutions to this important
12 drawback of COCs. We have used the term ‘missed pills’ to describe inconsistent COC use,
13 defined as missing one or more pills per 28-day cycle⁵.

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1 THE PILL AND ITS INCONSISTENT USE

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3 More than 100 million women worldwide used COCs in 2009, according to the United
4 Nations, equating to an 8.8% contraceptive prevalence among women of reproductive age⁶:
5 18.0% in developed countries alone (up to 59% in Portugal)⁷. In 2008, a study assessed
6 women's contraceptive practices and sexual behaviour across 14 European countries⁸. COCs
7 were the most popular contraception method, with usage rates highest in France (49%) and
8 the Czech Republic (44%), and lowest in Russia, the Baltic States and Spain (15–18%). The
9 study concluded that differences in usage may reflect socio-historical developments and
10 availability of contraception⁸. In late 2012, a 'pill scare' (mainly based on the higher risk of
11 venous thromboembolism (VTE) associated with 3rd- and 4th-generation COCs compared to
12 2nd-generation COCs) changed many women's perception of COCs. In France, a national
13 survey from 2010-2013 showed a 9% reduction in use of 3rd- and 4th-generation COCs and
14 was not compensated by increased use of 2nd-generation COCs (23% in 2013 versus 22% in
15 2010)⁹. In 2013, 229,000 abortions were conducted in France, a rise of 4.5% on 2012¹⁰:
16 similar outcomes were observed after the 1995 pill scare in Great Britain¹¹.

17

18 Forgetting one or more oral contraceptive tablets per cycle is common, regardless of age, but
19 adolescents have the highest risk of non-compliance⁴. They reportedly forget an average of
20 three pills per cycle, with discontinuation rates up to 50% during the first three months of
21 use¹². In a study comparing acceptability of the vaginal contraceptive ring to COCs, 12%
22 (8/65) of adolescents reported they forgot the pill and 1.5% (1/65) reported forgetting the
23 ring¹³. In women aged 18 or older, 10% to 51% miss at least three pills a month, depending
24 on electronic or self-reported data¹⁴. One study found 47% of women miss ≥ 1 pill per cycle
25 and 22% at least two pills per cycle⁴. A European survey showed that 19% of women aged 16

1 to 30 years missed one or more pills per cycle, increasing the risk of unintended pregnancy by
2 2.6 times compared to those who took COCs consistently¹⁵. In the United States, the
3 probability of pregnancy during the first year of perfect use (i.e. following the directions for
4 use) was estimated at 0.3%. Failure rates reached 9% with typical use, including inconsistent
5 and incorrect use^{16,17}.

6

7

8 REASONS FOR 'MISSED PILL'

9

10 COC compliance rates are similar to those for long-term treatments for chronic
11 conditions^{4,18,19}. Both are influenced by patient, environmental and clinician factors¹⁹. COC
12 regimens also have unique characteristics¹⁹: they are generally preventive rather than curative,
13 and COC users seldom receive ongoing reinforcement, whereas treatment management for
14 chronic conditions may provide symptom relief leading to positive feedback^{20,21}. COC users
15 have several treatment choices whereas patients treated for a specific condition often have
16 limited or no choice²⁰. Also, contraceptive decisions may be affected by interactions between
17 sexual partners, whereas usually just one patient is involved when a disease-related drug is
18 prescribed²⁰. Therefore, studying contraceptive compliance is more complex compared with
19 compliance with other medical regimens^{20,21}.

20

21 Women who do not establish a routine or do not succeed in associating COC intake with
22 another daily activity, such as applying make-up or brushing teeth, are 4.6 times more likely
23 to miss two or more pills per month and 3.3 times more likely to be inconsistent users
24 compared with women who have a routine¹⁵. In addition, women with little or no

1 understanding of COCs and their usage are 2.4 times more likely to miss two or more pills per
2 cycle than more informed women¹⁵.

3

4 Occurrence of side effects is the primary predictor for early discontinuations¹⁵. Increased risk
5 of missing a pill is associated with women's lack of involvement in choosing a contraceptive
6 method²², lack of a regular sex partner, limited support from a partner or low socioeconomic
7 status^{15,23}. Cultural aspects can also affect compliance: myths and misinformation are often
8 passed down the generations¹⁸.

9

10 Age and the type of physician prescribing the contraceptive were not significantly related to
11 consistent pill use¹⁵. However, experiencing benefits associated with COC, such as reduced
12 cramping and bleeding, may improve compliance.²⁴

13

14 In adolescents, psychosocial characteristics including low evaluation of personal health,
15 previous abortion and multiple sexual partners greatly influence compliance²⁵. Some
16 adolescents might not want their future threatened by an unwanted pregnancy, yet may
17 continue to seek personal self-fulfilment through childbearing²⁵. 'Magical thinking' is also
18 common: it helps maintain a shield of perceived low susceptibility to pregnancy¹⁸.

19

20 In a 2005 American study, the three most frequent reasons for missed pills given by the 141
21 COC users were 'away from home' (12.9%), 'forgot' (12.9%), and 'no new pack' (10.5%)²⁶.
22 If 'unavailable' was given as the reason for missing pills, one missed pill day was more likely
23 to be followed by another (44.3%). If the reason was physiological (i.e. health reasons, side
24 effects or sleep disturbances), the likelihood of missed pills on consecutive days was only

1 10.7%. The likelihood was significantly increased in case of ‘work pressures’ (19.3%) and
2 ‘no new pill pack’ (21.9%)²⁶.

3
4 In a 2013 Spanish multicentre study, forgetfulness was the main reason for omission/delay of
5 using COCs (74.9%) among 8,762 women aged 18-28 years, followed by having little
6 experience of their chosen contraceptive method²³. Remembering to use COCs was more
7 difficult on vacation (28.2%), weekends (34.8%), after going out the previous night (15.9%),
8 or on short trips (11.2%) than on weekdays (9.4%)²³.

9

10

11 MISSED PILLS AND OVULATION

12

13 Estrogen and, above all, progestin in COCs prevent ovulation by inhibiting gonadotropin
14 secretion via a negative feedback effect on the hypothalamo-pituitary axis²⁷⁻³⁰. The
15 contraceptive efficacy is essentially provided by the progestin component, which primarily
16 suppresses luteinizing hormone (LH) secretion necessary for ovulation^{28,30}. The estrogenic
17 component suppresses follicle-stimulating hormone (FSH) secretion, preventing the selection
18 of a dominant follicle²⁸. Another important role of estrogen and progestin is to stabilize the
19 endometrium and prevent unwanted breakthrough bleeding²⁸.

20

21 Although very effective in preventing pregnancy if correctly and consistently used, COCs do
22 not lead to complete ovarian suppression^{31,32}. Follicle growth and concomitant estradiol
23 production usually occur during the hormone-free interval (HFI), first week of medication, or
24 when COCs are missed³³⁻³⁵. Studies have shown a gradual decline of gonadotropins in the
25 first week of pill intake, which leads to suppression of non-dominant follicle development³⁶.

1 However, dominant follicles present on the first day the pill is taken can still increase in
2 diameter³⁶, so the potential to ovulate remains²⁹.

3

4 A study looked at serum pituitary and ovarian hormone levels during the 7-day HFI among
5 six different COC formulations³⁷. A greater dose-response suppression of LH, FSH, and
6 estradiol was found on day 1 of the HFI, with 30- or 35- μ g EE COCs than 20 μ g EE COCs.

7 Higher doses of EE were associated with a more rapid increase in gonadotropin levels from
8 day 1 to day 7 of the HFI; hormone levels during the HFI were not changed by the type and
9 dose of 19-norsteroid progestin³⁷.

10

11 Increasing the number of active pills per cycle or adding EE-only pills to shorten the HFI to 3
12 or 4 days diminishes FSH, LH and estradiol levels^{32,38}. This can provide greater pituitary-
13 ovarian inhibition, potentially reducing the risk of ovulation and common withdrawal
14 symptoms^{29,31,32,36,39}. More suppression of ovarian follicular activity is possible by
15 eliminating the HFI completely^{34,40}.

16

17 Ovarian suppression increases with the number of pills already taken, with maximum
18 suppression often encountered at the end of the COC cycle⁴¹. After achieving maximum
19 suppression (i.e. active pills taken for seven consecutive days), theoretically up to seven pills
20 can be omitted (the 7-day HFI) without affecting contraceptive efficacy⁴². Risk of pregnancy
21 after missing pills depends on when and how many pills are missed⁴³. The first week of the
22 COC cycle is critical⁴⁴. Evidence suggests missing pills on days not adjacent to the HFI is
23 less critical to missing pills on adjacent days⁴². Eliminating the HFI when one or more days
24 of COCs are missed in Week 2 or Week 3 may reduce the risk of unplanned pregnancy⁴⁵.

1 However, missing three or more pills in a row during Week 3 is likely to impair contraceptive
2 effectiveness, because the HFI comes immediately after Week 3⁴⁵.

3

4

5 GUIDELINES ABOUT MISSED COCS

6

7 Guidelines are conflicting, probably leading to their low acceptance rate by physicians and
8 COC users⁴⁶. Revised recommendations were developed based mainly on the evidence
9 reviewed in 2008 by the WHO Expert Working Group, a Cochrane review and the Society of
10 Obstetrics and Gynaecology of Canada⁴³. The missed pill window was changed from 12
11 hours to 24 hours⁴³. The number of pills missed and the time in the cycle when this occurs
12 are crucial for considering risk of contraceptive failure⁴³. Contraceptive cover is provided:
13 the user should take the last pill missed, even if it means taking two pills in one day, and
14 continue taking the rest of the pack as usual⁴³. Missing two or more pills (more than 48 hours
15 late) may affect the contraceptive cover, except in the second week of the pack and could
16 require emergency contraception⁴³.

17

18

19 HOW CAN THE 'MISSED PILL ISSUE' BE ADDRESSED?

20

21 Several strategies have been proposed to improve contraceptive compliance⁴. HCPs must
22 ensure patients understand the correct usage of COCs and help women with their choice,
23 based on background, individual needs and concerns⁴. Talking about establishing a regular
24 pill-taking routine, discussing possible side effects associated with pill use, providing clear
25 instructions (including missed pill guidance), and using follow-up contact to look for signs of

1 non-compliance are all strategies that may prove helpful, particularly with adolescents who
2 may sporadically use COCs^{4,21}.

3

4 COC users should take the pill at a regular time, preferably as part of a daily routine such as
5 applying make-up, carefully read the instructions that come with the pill package, and know
6 what to do if pills are missed⁴.

7

8 There are options for women who want reliable contraception, but have poor compliance:
9 long-acting reversible contraceptives (LARCs), such as an intrauterine system (IUS) and
10 implants, do not depend on daily pill-taking^{3,47}. LNG IUS is often considered close to an
11 ‘ideal’ contraceptive, although $\geq 25\%$ of women discontinue this method within the first year⁴⁸
12 and at five years the discontinuation rate reaches 60%, mostly due to bleeding problems⁴⁹.

13

14

15 CAN A COC WITH A LONG HALF-LIFE PROGESTIN AND SHORT HFI IMPROVE
16 THE MISSED PILL ISSUE?

17

18 Follicular maturation is most likely to occur during an HFI or following a missed pill^{29,36}. In
19 2004, a cohort study found that women using pills in a continuous 28-day cycle missed fewer
20 pills in the vulnerable first week than those using a traditional 21-day regimen⁴⁴. The study
21 concluded that continuous (everyday) cycle regimens provide an undeniable benefit,
22 eliminating the risk of forgetting during the week of discontinuation between two blister
23 packs⁴⁴. In contrast, a 2014 Cochrane study found no statistically significant difference in
24 compliance rates between traditional monthly cyclic dosing and extended cycles⁵⁰. It has
25 been argued that 28-day packs are much simpler and cause less confusion than 21-day

1 packs^{21,51}. However, there is variation in the onset of withdrawal bleeding and some women
2 may start the next cycle as late as 8-10 days after the previous packet²¹.

3
4 Additional use of a progestin with a long half-life was suggested to reduce the risk of
5 contraceptive failure during ‘typical use’, which includes occasional missed pills¹⁶.

6 Knowledge of a drug’s elimination half-life is useful for making recommendations on how to
7 proceed if the patient has missed one or more doses⁵². In general, a single missed dose is less
8 problematic for a drug with a long half-life as it will lose therapeutic effect less rapidly than a
9 drug with a shorter half-life²⁷.

10

11 A variety of progestins, including testosterone-, progesterone-derived progestins, and
12 derivatives of progesterone are currently used in COCs. They differ in their biological effects
13 (in addition to the basic progestogenic effect), and their pharmacokinetic parameters,
14 including half-life (Table 1)⁵³⁻⁵⁶.

15

16 Drospirenone (DRSP) is a progestin with a half-life of 40 hours⁵⁴. In a study, which included
17 intentional dosing error days at the beginning of Cycle 3 (equivalent to missed pill days), it
18 was reported that ovarian suppression was more frequent in the 24/4 regimen group than in
19 the 21/7 regimen: 87.8% vs. 56.0% during Cycle 2 and 55.1% vs. 30.0% during Cycle 3,
20 respectively⁵⁷. The EE 24/4 regimen COC was also associated with less fluctuation of
21 endogenous estradiol⁵⁷. It was concluded that, under conditions of imperfect use, a 24-day
22 COC containing a progestin with a long half-life may offer better effectiveness than a 21-day
23 COC containing a progestin with a short half-life¹⁶.

24

1 Norgestrel acetate (NOMAC) is another progestin that exhibits a long elimination half-life
2 (46 hours) and is used in combination with estradiol (E2) to provide a monophasic regimen
3 COC, NOMAC/E2. NOMAC is a progesterone-derived progestin that binds almost
4 exclusively to the progesterone receptor and does not interfere with other steroid receptors⁵⁸⁻
5 ⁶⁰. In a 24-day regimen, NOMAC/E2 was associated with greater inhibition of follicular
6 growth and shorter duration of withdrawal bleeding than a 21-day regimen⁶¹. Withdrawal
7 bleeding duration was significantly shorter in the 24-day group⁶¹.

8
9 Following findings that a long half-life may offer greater flexibility in the event of a missed
10 dose compared with COCs containing progestins with shorter half-lives¹⁶, the summary of
11 product characteristics of the 24/4 regimen of DRSP/EE was updated in 2013 to extend the
12 time window for missed pills from 12 to 24 hours⁶². Two years later, the missed pill window
13 was also changed from 12 to 24 hours for the E2 pill NOMAC/E2⁶³.

14 15 CONCLUSION

16
17 Women using COCs differ from other patients in that they make the decision to use a
18 contraceptive to modulate a physiological process without medical indications¹⁸. Non-
19 compliance reveals the difficulties they experience with their daily use of the pill. In the
20 context of high prevalence of both pill omission and the subsequent risk of contraceptive
21 failure, improving COC use may be a responsibility shared among COC users, providers and
22 manufacturers. Shortening the HFI to 3 or 4 days, or even eliminating the HFI completely,
23 can reduce ovarian follicular activity and the risk of ovulation. Pharmacokinetics of COCs
24 and the scheme of combination are characteristics that should be considered. A progestin

1 with a longer half-life, as well as a shorter HFI, could contribute to greater effectiveness of
2 COCs under conditions of typical use.

3

4 ACKNOWLEDGEMENTS

5 This study was supported by Teva. The manuscript was prepared with writing and editorial
6 assistance from Jean-Louis Carsol, Daniel Loniewski and Tristan Blundell, all employed by
7 Publicis Life Brands International.

8

9 ***Declaration of interest:*** NC-B is a member of the European board of Teva/Theramex and of
10 the French board of Gedeon Richter. CJ is a consultant for MSD, Teva and HRA Pharma. IL
11 has a financial relationship (lecturer, member of advisory boards and/or consultant) with
12 MSD, Teva, Gedeon Richter, HRA Pharma and Nordic Pharma. P. L. has received lecture
13 fees, is member of advisory boards and/or consultant with Bayer, Effik, MSD and
14 TEVA/Theramex. REN has a financial relationship (lecturer, member of advisory boards
15 and/or consultant) with Bayer HealthCare, Boehringer Ingelheim, Eli Lilly, Gedeon Richter,
16 HRA Pharma, MSD, Novo Nordisk, Pfizer, Procter & Gamble, Shionogi and Teva. AP is a
17 member of the European Board of Teva without personal gain. CF has been a lecturer for
18 Teva and Bayer HealthCare and is a member of the European scientific advisory board of
19 Teva and Exelgyn.

20

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1 64. **Tables**

2

3 Table 1: Half-life of various progestins⁵⁴⁻⁵⁶. Half-lives can be given in a range of values for a
4 few progestins. Dienogest and nomegestrol acetate are used in combination with estradiol,
5 other progestins in combination with ethinylestradiol.

6

Progestins	Half-life (hours)
Norethisterone	5 – 12 ⁵⁴
Dienogest	11 ⁵⁴
Norgestimate	12 – 30 ⁵⁵
Gestodene	16 – 18 ⁵⁵
Levonorgestrel	20 ⁵⁴
Desogestrel	31 ⁵⁴
Chlormadinone acetate	34 – 36 ⁵⁶
Cyproterone acetate	38 ⁵⁵
Drospirenone	40 ⁵⁴
Nomegestrol acetate	46 ⁵⁴

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