Missed pills: frequency, reasons, consequences and solutions

Nathalie Chabbert-Buffet, Christian Jamin, Inaki Lete, Paloma Lobo, Rossella E. Nappi, Axelle Pintiaux, Günther Haüsler, Christian Fiala

Missed pills: frequency, reasons, consequences and solutions

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

[#] Department of Obstetrics and Gynaecology, APHP Tenon Hospital, Pierre and Marie Curie University, Paris, France; [‡]169, boulevard Haussmann, Paris, France; [*]Department of Obstetrics and Gynaecology, Araba University Hospital, Vitoria-Gasteiz, Spain; [§]Department of Obstetrics and Gynaecology, Infanta Sofía University Hospital, San Sebastián de los Reyes, Madrid, Spain; [^]Research Centre for Reproductive Medicine, Gynaecological Endocrinology and Menopause, IRCCS San Matteo Foundation, Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy; [$]Department of Obstetrics and Gynaecology, Citadelle Hospital, Liège University, Liège, Belgium; [**]Department of Gynaecology and Gynaecological Oncology, AKH-Wien, Vienna, Austria; and [†]Gynmed Ambulatorium, Vienna, Austria, and Department of Women's and Children's Health, Karolinska Institutet, Stockholm Sweden.

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

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.

INTRODUCTION

Fertility has been a concern for people throughout history. Pre-20th Century contraceptive methods included male condoms and coitus interruptus, and with the development of combined oral contraceptives (COCs) in the 1960s women gained more control[1]. However, the high contraceptive efficacy of COCs depends on regular daily intake[2,3] and compliance problems are common among all age groups[4]. Efforts were made to improve compliance (including easy use, minimal side effects and better tolerability), but with poor results[3].

In this narrative review we will summarize available data from the literature on missed pill occurrence and its consequences, as well as discuss available solutions to this important drawback of COCs. We have used the term 'missed pills' to describe inconsistent COC use, defined as missing one or more pills per 28-day cycle[5].

THE PILL AND ITS INCONSISTENT USE

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

Forgetting one or more oral contraceptive tablets per cycle is common, regardless of age, but adolescents have the highest risk of non-compliance[4]. They reportedly forget an average of three pills per cycle, with discontinuation rates up to 50% during the first three months of use[12]. In a study comparing acceptability of the vaginal contraceptive ring to COCs, 12% (8/65) of adolescents reported they forgot the pill and 1.5% (1/65) reported forgetting the ring[13]. In women aged 18 or older, 10% to 51% miss at least three pills a month, depending on electronic or self-reported data[14]. One study found 47% of women miss $\geq$1 pill per cycle and 22% at least two pills per cycle[4]. A European survey showed that 19% of women aged 16

to 30 years missed one or more pills per cycle, increasing the risk of unintended pregnancy by 2.6 times compared to those who took COCs consistently[15]. In the United States, the probability of pregnancy during the first year of perfect use (i.e. following the directions for use) was estimated at 0.3%. Failure rates reached 9% with typical use, including inconsistent and incorrect use[16,17].

REASONS FOR 'MISSED PILL'

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

Women who do not establish a routine or do not succeed in associating COC intake with another daily activity, such as applying make-up or brushing teeth, are 4.6 times more likely to miss two or more pills per month and 3.3 times more likely to be inconsistent users compared with women who have a routine[15]. In addition, women with little or no

understanding of COCs and their usage are 2.4 times more likely to miss two or more pills per cycle than more informed women[15].

Occurrence of side effects is the primary predictor for early discontinuations[15]. Increased risk of missing a pill is associated with women's lack of involvement in choosing a contraceptive method[22], lack of a regular sex partner, limited support from a partner or low socioeconomic status[15,23]. Cultural aspects can also affect compliance: myths and misinformation are often passed down the generations[18].

Age and the type of physician prescribing the contraceptive were not significantly related to consistent pill use[15]. However, experiencing benefits associated with COC, such as reduced cramping and bleeding, may improve compliance.[24]

In adolescents, psychosocial characteristics including low evaluation of personal health, previous abortion and multiple sexual partners greatly influence compliance [25]. Some adolescents might not want their future threatened by an unwanted pregnancy, yet may continue to seek personal self-fulfilment through childbearing[25]. 'Magical thinking' is also common: it helps maintain a shield of perceived low susceptibility to pregnancy[18].

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

10.7%. The likelihood was significantly increased in case of 'work pressures' (19.3%) and 'no new pill pack' (21.9%)[26].

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

MISSED PILLS AND OVULATION

Estrogen and, above all, progestin in COCs prevent ovulation by inhibiting gonadotropin secretion via a negative feedback effect on the hypothalamo-pituitary axis[27-30]. The contraceptive efficacy is essentially provided by the progestin component, which primarily suppresses luteinizing hormone (LH) secretion necessary for ovulation[28,30]. The estrogenic component suppresses follicle-stimulating hormone (FSH) secretion, preventing the selection of a dominant follicle[28]. Another important role of estrogen and progestin is to stabilize the endometrium and prevent unwanted breakthrough bleeding[28].

Although very effective in preventing pregnancy if correctly and consistently used, COCs do not lead to complete ovarian suppression[31,32]. Follicle growth and concomitant estradiol production usually occur during the hormone-free interval (HFI), first week of medication, or when COCs are missed[33-35]. Studies have shown a gradual decline of gonadotropins in the first week of pill intake, which leads to suppression of non-dominant follicle development[36].

However, dominant follicles present on the first day the pill is taken can still increase in diameter[36], so the potential to ovulate remains[29].

A study looked at serum pituitary and ovarian hormone levels during the 7-day HFI among six different COC formulations[37]. A greater dose-response suppression of LH, FSH, and estradiol was found on day 1 of the HFI, with 30- or 35-μg EE COCs than 20μg EE COCs. Higher doses of EE were associated with a more rapid increase in gonadotropin levels from day 1 to day 7 of the HFI; hormone levels during the HFI were not changed by the type and dose of 19-norsteroid progestin[37].

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

Ovarian suppression increases with the number of pills already taken, with maximum suppression often encountered at the end of the COC cycle[41]. After achieving maximum suppression (i.e. active pills taken for seven consecutive days), theoretically up to seven pills can be omitted (the 7-day HFI) without affecting contraceptive efficacy[42]. Risk of pregnancy after missing pills depends on when and how many pills are missed[43]. The first week of the COC cycle is critical[44]. Evidence suggests missing pills on days not adjacent to the HFI is less critical to missing pills on adjacent days[42]. Eliminating the HFI when one or more days of COCs are missed in Week 2 or Week 3 may reduce the risk of unplanned pregnancy[45].

However, missing three or more pills in a row during Week 3 is likely to impair contraceptive effectiveness, because the HFI comes immediately after Week 3[45].

GUIDELINES ABOUT MISSED COCS

Guidelines are conflicting, probably leading to their low acceptance rate by physicians and COC users[46]. Revised recommendations were developed based mainly on the evidence reviewed in 2008 by the WHO Expert Working Group, a Cochrane review and the Society of Obstetrics and Gynaecology of Canada[43]. The missed pill window was changed from 12 hours to 24 hours[43]. The number of pills missed and the time in the cycle when this occurs are crucial for considering risk of contraceptive failure[43]. Contraceptive cover is provided: the user should take the last pill missed, even if it means taking two pills in one day, and continue taking the rest of the pack as usual[43]. Missing two or more pills (more than 48 hours late) may affect the contraceptive cover, except in the second week of the pack and could require emergency contraception[43].

HOW CAN THE 'MISSED PILL ISSUE' BE ADDRESSED?

Several strategies have been proposed to improve contraceptive compliance[4]. HCPs must ensure patients understand the correct usage of COCs and help women with their choice, based on background, individual needs and concerns[4]. Talking about establishing a regular pill-taking routine, discussing possible side effects associated with pill use, providing clear instructions (including missed pill guidance), and using follow-up contact to look for signs of

non-compliance are all strategies that may prove helpful, particularly with adolescents who may sporadically use COCs[4,21].

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

There are options for women who want reliable contraception, but have poor compliance: long-acting reversible contraceptives (LARCs), such as an intrauterine system (IUS) and implants, do not depend on daily pill-taking[3,47]. LNG IUS is often considered close to an 'ideal' contraceptive, although ≥25% of women discontinue this method within the first year[48] and at five years the discontinuation rate reaches 60%, mostly due to bleeding problems[49].

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

Follicular maturation is most likely to occur during an HFI or following a missed pill[29,36]. In 2004, a cohort study found that women using pills in a continuous 28-day cycle missed fewer pills in the vulnerable first week than those using a traditional 21-day regimen[44]. The study concluded that continuous (everyday) cycle regimens provide an undeniable benefit, eliminating the risk of forgetting during the week of discontinuation between two blister packs[44]. In contrast, a 2014 Cochrane study found no statistically significant difference in compliance rates between traditional monthly cyclic dosing and extended cycles[50]. It has been argued that 28-day packs are much simpler and cause less confusion than 21-day

packs[21,51]. However, there is variation in the onset of withdrawal bleeding and some women may start the next cycle as late as 8-10 days after the previous packet[21].

Additional use of a progestin with a long half-life was suggested to reduce the risk of contraceptive failure during 'typical use', which includes occasional missed pills[16]. Knowledge of a drug's elimination half-life is useful for making recommendations on how to proceed if the patient has missed one or more doses[52]. In general, a single missed dose is less problematic for a drug with a long half-life as it will lose therapeutic effect less rapidly than a drug with a shorter half-life[27].

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

Drospirenone (DRSP) is a progestin with a half-life of 40 hours[54]. In astudy, which included intentional dosing error days at the beginning of Cycle 3 (equivalent to missed pill days), it was reported that ovarian suppression was more frequent in the 24/4 regimen group than in the 21/7 regimen: 87.8% vs. 56.0% during Cycle 2 and 55.1% vs. 30.0% during Cycle 3, respectively[57]. The EE 24/4 regimen COC was also associated with less fluctuation of endogenous estradiol[57]. It was concluded that, under conditions of imperfect use, a 24-day COC containing a progestin with a long half-life may offer better effectiveness than a 21-day COC containing a progestin with a short half-life[16].

Nomegestrol acetate (NOMAC) is another progestin that exhibits a long elimination half-life (46 hours) and is used in combination with estradiol (E2) to provide a monophasic regimen COC, NOMAC/E2. NOMAC is a progesterone-derived progestin that binds almost exclusively to the progesterone receptor and does not interfere with other steroid receptors[58-60]. In a 24-day regimen, NOMAC/E2 was associated with greater inhibition of follicular growth and shorter duration of withdrawal bleeding than a 21-day regimen[61]. Withdrawal bleeding duration was significantly shorter in the 24-day group[61].

Following findings that a long half-life may offer greater flexibility in the event of a missed dose compared with COCs containing progestins with shorter half-lives[16], the summary of product characteristics of the 24/4 regimen of DRSP/EE was updated in 2013 to extend the time window for missed pills from 12 to 24 hours[62]. Two years later, the missed pill window was also changed from 12 to 24 hours for the E2 pill NOMAC/E2[63].

CONCLUSION

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

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

ACKNOWLEDGEMENTS

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

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

REFERENCES

1. Planned Parenthood. A history of birth control methods. Knowles J. In the Katharine Dexter McCormick Library and the Education Division of Planned Parenthood Federation of America. New York 2012. Accessed on 22 January 2016 from: https://www.plannedparenthood.org/files/2613/9611/6275/History_of_BC_Methods.pdf
2. Grimes DA. Forgettable contraception. *Contraception* 2009;80:497–99.
3. Halpern V, Lopez LM, Grimes DA, et al. Strategies to improve adherence and acceptability of hormonal methods of contraception. *Cochrane Database Syst Rev* 2013;10:CD004317.
4. Rosenberg M, Waugh MS. Causes and consequences of oral contraceptive noncompliance. *Am J Obstet Gynecol* 1999;180:276–79.
5. Hall KS, White KO, Reame N, et al. Studying the use of oral contraception: a review of measurement approaches. *J Womens Health (Larchmt)* 2010;19:2203–10.
6. Christin-Maitre S. History of oral contraceptive drugs and their use worldwide. *Best Pract Res Clin Endocrinol Metab* 2013;27:3–12.
7. World Contraceptive Patterns 2011. Accessed on 22 January 2016 from: http://www.un.org/esa/population/publications/contraceptive2011/wallchart_front.pdf
8. Cibula D. Women’s contraceptive practices and sexual behaviour in Europe. *Eur J Contracept Reprod Health Care* 2008;13:362–75.
9. Bajos N, Rouzaud-Cornabas M, Panjo H, Bohet A, et al. The French pill scare: towards a new contraceptive model? *Pop Soc* 2014;511.
10. Vilain A, Mouquet M-C. Les interruptions volontaires de grossesse en 2013. *Etudes & Résultats (DREES)* 2015; 0924. [Article in French]
11. Dillner L. Pill scare linked to rise in abortions. *BMJ* 1996;312:996.
12. Balassone ML. Risk of contraceptive discontinuation among adolescents. *J Adolesc Health Care* 1989;10:527–33.
13. Stewart FH, Brown BA, Raine TR. Weitz TA, et al. Adolescent and young women's experience with the vaginal ring and oral contraceptive pills. *J Pediatr Adolesc Gynecol* 2007;20:345–51.
14. Potter L, Oakley D, de Leon-Wong E, et al. Measuring compliance among oral contraceptive users. *Fam Plann Perspect* 1996;28:154–58.
15. Rosenberg MJ, Waugh MS, Long S. Unintended pregnancies and use, misuse and discontinuation of oral contraceptives. *J Reprod Med* 1995;40:355–60.

16. Dinger J, Minh TD, Buttmann N, et al. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol* 2011;117:33–40.

17. Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.

18. Cramer JA. Compliance with contraceptives and other treatments. *Obstet Gynecol* 1996;88:4S–12S.

19. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med* 2008;31:213–24.

20. Whelan EM. Compliance with contraceptive regimens. *Stud Fam Plann* 1974;5:349–55.

21. Global Library of Women's Medicine. The educational platform for FIGO (The International Federation of Gynecology and Obstetrics). Culwell, K, Hillard, P. Patient education and contraceptive compliance. (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10378. Accessed on 22 January 2016 from: http://www.glowm.com/section_view/heading/Patient%20Education%20and%20Contraceptive%20Compliance/item/377

22. Moreau C, Bouyer J, Gilbert F, et al. Social, demographic and situational characteristics associated with inconsistent use of oral contraceptives: evidence from France. *Perspect Sex Reprod Health* 2006;38:190–96.

23. Martínez-Astorquiza-Ortiz de Zarate T, Díaz-Martín T, Martínez-Astorquiza-Corral T, et al. Evaluation of factors associated with noncompliance in users of combined hormonal contraceptive methods: a cross-sectional study: results from the MIA study. *BMC Womens Health* 2013;13:38.

24. Robinson J, Plichta S, Weisman C, et al. Dysmenorrhea and use of oral contraceptives in adolescent women attending a family planning clinic. *Am J Obstet Gynecol* 1992;166: 578–583.

25. Durant RH, Jay MS, Linder CW, *et al*. Influence of psychosocial factors on adolescent compliance with oral contraceptives. *J Adolesc Health Care* 1984;5:1–6.

26. Smith JD, Oakley D. Why do women miss oral contraceptive pills? An analysis of women's self-described reasons for missed pills. *J Midwifery Womens Health* 2005;50:380–85.

27. Wan LS, Ganguly M, Weiss G. Pituitary response to LHRH stimulation in women on oral contraceptives: a followup dose response study. *Contraception* 1981;24:229–34.

28. Speroff L, Glass RH, Kase NG. Oral contraception. In Clinical Gynecologic Endocrinology and Infertility 6th ed. Lippincott Williams & Wilkins 1999.

29. Baerwald AR, Pierson RA. Ovarian follicular development during the use of oral contraception: a review. *J Obstet Gynaecol Can* 2004;26:19–24.

30. Bitzer J, Simon JA. Current issues and available options in combined hormonal contraception. *Contraception* 201;84:342–56.
31. Spona J, Elstein M, Feichtinger W, *et al*. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996;54:71–7.
32. Willis SA, Kuehl TJ, Spiekerman AM, *et al*. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception* 2006;74:100–3.
33. Fauser BC, Van Heusden AM. Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocr Rev* 1997;18:71–106.
34. Kuehl TJ, Speikermann AM, Willis SA, *et al*. Pituitary-ovarian hormone levels and symptoms in oral contraceptive users: comparison of a 21/7-day and extended regimen. *J Reprod Med* 2008;53:266–70.
35. Vandever MA, Kuehl TJ, Sulak PJ, *et al*. Evaluation of pituitary-ovarian axis suppression with three oral contraceptive regimens. *Contraception* 2008;77:162–70.
36. van Heusden AM, Fauser BC. Residual ovarian activity during oral steroid contraception. *Hum Reprod Update* 2002;8:345–58.
37. Cho M, Atrio J, Lim AH, *et al*. Pituitary and ovarian hormone activity during the 7-day hormone-free interval of various combined oral contraceptive regimens. *Contraception* 2014;90:94–6.
38. Killick SR, Bancroft K, Oelbaum S, *et al*. Extending the duration of the pill-free interval during combined oral contraception. *Adv Contracept* 1990;6:33–40.
39. Sullivan H, Furniss H, Spona J, *et al*. Effect of 21-day and 24-day oral contraceptives decreases follicular development. *Fertil Steril* 1999;72:115–20.
40. Schlaff WD, Lynch AM, Hughes HD, *et al*. Manipulation of the pill-free interval in oral contraceptive pill users: the effects on follicular suppression. *Am J Obstet Gynecol* 2004;190:943–51.
41. Smith SK, Kirkman RJ, Arce BB, *et al*. The effect of deliberate omission of Trinordiol or Microgynon on the hypothalamo-pituitary-ovarian axis. *Contraception* 1986;34:513–22.
42. Curtis KM, Chrisman CE, Mohllajee AP, *et al*. Effective use of hormonal contraceptives: Part I: Combined oral contraceptive pills. *Contraception* 2006;73:115–24.
43. MHRA UK public assessment report. Combined oral contraceptives (the Pill): when to start taking the Pill, and missed pill advice. London: The Medicines and Healthcare products Regulatory Agency, 2011. Accessed on 22 January 2016 from: http://www.mhra.gov.uk/safety-public-assessment-reports/CON120481

44. Aubeny E, Buhler M, Colau JC, *et al*. The Coraliance study: non-compliant behavior. Results after a 6-month follow-up of patients on oral contraceptives. *Eur J Contracept Reprod Health Care* 2004;9:267–77.

45. Guilbert E, Black A, Dunn S, *et al*. Missed hormonal contraceptives: new recommendations. *J Obstet Gynaecol Can* 2008;30:1050–77.

46. Jamin C, André G, Audebert A, *et al*. Oublis de la contraception hormonale : réflexions sur leur prise en charge en pratique quotidienne. *Gynecol Obstet Fertil* 2011 ; 39 : 644–55. [Article in French]

47. Stoddard A, McNicholas C, Peipert JF. Efficacy and safety of long-acting reversible contraception. *Drugs* 2011;71:969–80.

48. Diaz J, Bahamondes L, Monteiro I, *et al*. Acceptability and performance of the levonorgestrel-releasing intrauterine system (Mirena) in Campinas, Brazil. *Contraception* 2000;62:59–61.

49. Cox M, Tripp J, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 5-year report. *J Fam Plann Reprod Health Care* 2002;28:73–7.

50. Edelman A, Micks E, Gallo MF, *et al*. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database Syst Rev* 2014;7:CD004695. doi: 10.1002/14651858.CD004695.pub3.

51. Finlay IG, Scott MG. Patterns of contraceptive pill taking in an inner city practice. *Br Med J (Clin Res Ed)* 1986;293:601–2.

52. Gilbert A, Roughead L, Sansom L. I've missed a dose; what should I do? *Aust Prescr* 2002;1:16–18.

53. Schindler AE, Campagnoli C, Druckmann R, *et al*. Classification and pharmacology of progestins. *Maturita* 2008;61:171–80.

54. eMC. Accessed on 22 January 2016 from: https://www.medicines.org.uk/emc/

55. Drug Bank. Accessed on 22 January 2016 from: http://www.drugbank.ca/

56. Bouchard P. Chlormadinone acetate (CMA) in oral contraception--a new opportunity. *Eur J Contracept Reprod Health Care* 2005;10 Suppl 1:7–11.

57. Klipping C, Duijkers I, Trummer D, *et al*.Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen . *Contraception* 2008;78:16–25..

58. Catherino WH, Jordan VC. Nomegestrol acetate, a clinically useful 19 norprogesterone derivative which lacks estrogenic activity. *J Steroid Biochem Mol Biol* 1995;55:239–46.

59. Kuhl H. Comparative pharmacology of newer progestogens. *Drugs* 1996;51:188–215.

60. Sitruk-Ware R. Pharmacological profile of progestins. *Maturitas* 2008;61:151–57.

61. Christin-Maitre S, Serfaty D, Chabbert-Buffet N, *et al*. Comparison of a 24-day and a 21-day pill regimen for the novel combined oral contraceptive, nomegestrol acetate and 17b-estradiol (NOMAC/E2): a double-blind, randomized study. *Hum Reprod* 2011;26:1338–47.

62. Public assessment report of the Medicines Evaluation Board in the Netherlands. Yaz 24+4, film-coated tablets 0.02 mg/3 mg Bayer B.V., the Netherlands ethinylestradiol/drospirenone, 2013. Accessed on 22 January 2016 from: http://db.cbg-meb.nl/Pars/h33842.pdf

63. European Medicines Agency. Zoely Procedural steps taken and scientific information after the authorization. London: EMA/513508/2015. Accessed on 22 January 2016 from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/001213/WC500118356.pdf

64. Tables

Table 1: Half-life of various progestins[54-56]. Half-lives can be given in a range of values for a few progestins. Dienogest and nomegestrol acetate are used in combination with estradiol, other progestins in combination with ethinylestradiol.

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]