Curr Obstet Gynecol Rep (2016) 5:13–19
DOI 10.1007/s13669-016-0143-5

FAMILY PLANNING (A. BURKE, SECTION EDITOR)

The Pill at 56 and Counting: Still Contracepting After All These Years

Maude Côté-Leduc[1] · **Geneviève Roy**[2]

Published online: 11 February 2016

Abstract Oral contraceptives are one of the most popular contraceptive methods worldwide. They offer many benefits other than contraceptive efficacy; women also choose the pill for medical or personal reasons. While the pill is extremely safe, there are still concerns about side effects and complications, difficulties with cycle control and compliance. Several approaches have been developed to improve overall experience with oral contraceptives, including lowering doses of estrogen to diminish side effects, though that can create more bleeding irregularities and possibly reduce efficacy. Modifications of pill scheduling by proposing extended or continuous cycle have shown good results decreasing symptoms related to menses. Contraceptive pills can effectively decrease certain premenstrual and menstrual symptoms. Finally, the use of new technologies to try to increase adherence is being explored, though without convincing results so far.

Keywords Low-dose estrogen COC · Pearl Index · Extended-cycle COC · Adherence · New technologies

This article is part of the Topical Collection on *Family Planning*

✉ Geneviève Roy
genipou14@hotmail.com

[1] Department of Family Medicine, University of Montreal, Montreal, QC, Canada

[2] Department of Obstetrics and Gynecology, University of Montreal, Montreal, QC, Canada

Introduction

Since its introduction in the 1960s, the contraceptive pill has gained so much popularity that approximately 9 % of women worldwide use it. It is the most commonly used method in the developed world and the third most common in the developing world. Contraception offers women the possibility to plan their families and increase their chances to achieve higher education and improved socioeconomic status [1]. In recent years, much research and funding has been devoted to long acting reversible contraceptives (LARCs), i.e., intrauterine devices and implants. They do offer many advantages over oral contraceptives (OCs) such as very high efficacy and continuation. Still, some women will prefer short acting reversible methods such as the pill, the patch, or the ring for diverse reasons. A wide array of methods must remain available in order to meet women's health needs, contraceptive efficacy being one of them. Other characteristics of the pill can appeal to some women based on their specific health needs [2]. Indeed, OCs provide many health benefits other than contraception such as listed in Table 1 [3].

Use of COC has been related to increased cardiovascular risks such as venous thromboembolism. It is also associated with side effects related to both estrogen and progestins. Thrombotic risks of COC have been well described elsewhere and are not the focus of this paper. In the last 50 years, efforts have been made to improve the side effect profile and improve safety, while maintaining contraceptive efficacy. Many strategies have been explored, such as decreased estrogen dosage, new types of progestins, different administration schedules, and use of technology to improve adherence. Efforts have also been made to increase access to oral contraceptives. We will address some of these in the following article.

Table 1 Which non-contraceptive benefits can be obtained with combined hormonal contraceptive?

Which non-contraceptive benefits can be obtained with combined hormonal contraceptive?	
Menstrual advantages	Non-menstrual advantages
•Regulation of menstrual cycle	•Reduction of acne
•Diminution of menorrhagia (and bleeding from fibroids)	•Protects against ovarian, endometrial, and colorectal cancer
•Relief of dysmenorrhea (and pelvic pain from endometriosis)	•Improvement of bone density
•Possible amenorrhea for quality of life	•Treatment of premenstrual syndrome
	•Decreases menstrual migraines

Adapted from ACOG practice bulletin no 110: noncontraceptive uses of contraceptives. Obstet Gynecol, 2010; 115(1): 206 [3]

Low-Dose Estrogen Oral Contraceptives and Contraceptive Efficacy

The first oral contraceptives contained as much as 150 μg of ethinyl estradiol (EE) [1]. It was believed that such a dose was necessary to gain sufficient contraceptive efficacy. After realizing that much of the contraceptive efficacy was in fact attributable to the progestin component of the combined pill, and that estrogen was associated with adverse events such as thromboembolic, cerebrovascular incidents, and myocardial infarction, efforts have been made to reduce EE dose without compromising effectiveness. Studies subsequently showed a reduction of side effects and complications such as nausea, headaches, breast tenderness, bloating, and thromboembolic events.

Lowering EE doses below 50 μg has indeed improved safety and side effect profile of the pill. There has been concern that lowering too much could compromise cycle control, which in turn can lead to discontinuation. A 2013 Cochrane review assessed randomized controlled trial (RCT)'s comparing oral contraceptive pills containing 20 μg of EE with those having >20 μg of EE in terms of effectiveness, discontinuation, bleeding patterns, and side effects [4]. Unfortunately, the majority of the 21 included studies were underpowered to compare effectiveness or adverse events. The only significant difference was that women on 20 μg of estrogen had "higher rates of bleeding pattern disruptions," including infrequent as well as frequent and prolonged bleeding. Most trials compared pills with different types of progestins, which may also compromise cycle control [4].

Efforts are being made to further reduce the dose of estrogen in order to achieve the goals previously mentioned. A new COC with only 10 mcg of EE was approved in 2010 in the USA and in 2013 in Canada. The dosing schedule consists of a 24/2/2 cycle: the first 24 pills contain 1 mg of norethindrone and 10 mcg of EE, the next two pills contain only 10 mcg of EE and the last two pills are inactive tablets or with 75 mg of ferrous fumarate in the USA [5, 6].

The phase III study of this COC was a non-comparative, open-label, multicenter study (68 centers in 21 American states) (5). The population included 1660 healthy women aged 18 to 45 years old with a BMI of less than 35 kg/m^2. The primary outcome was efficacy. Secondary outcomes were intra-cyclic bleeding, safety, and tolerability. The study was completed over 13 cycles. There was a discontinuation rate of 41.7 % [5]. Most (85.9 %) participants had intra-cyclic bleeding or spotting. These irregularities were more common in new users but had a tendency to decrease with use (from 3.2 days in cycle 2 to 1.8 days in cycle 13). Length and heaviness of withdrawal bleeding also decreased over the course of the study. There were 28 pregnancies in the 18–35-year-old group over a total of 12,266 at-risk cycles, calculating a Pearl Index (PI) of 2,92, including women who did not take the drug correctly [5, 6, 7•]. This value appears somewhat higher than the PIs calculated in previous COC studies.

Effectiveness of Oral Contraceptives: the Pearl Index

For a few years now, there have been questions as to why the Pearl Index for pills has tended to increase over time. Is it indeed because new COCs with less EE are less effective, or are there other explanations? Several authors have studied and commented on this issue.

First, studies are often difficult to compare. There are many differences when comparing participants from one study to another. These can include compliance, frequency of intercourse, age, fertility of both user and partner, motivation to avoid pregnancy, switcher vs. new user status and demographic characteristics (race/ethnicity, socioeconomic status, marital status, education and religion) [8•]. These characteristics have not been similarly controlled across studies. In 2014, Gerlinger compared, with a matching propensity score, four studies that included 6602 subjects [9] (one with a contraceptive patch, for which the PI was 3,56 and three other COC studies with respective PIs of 0,72 [10]), 0,79 [11]) and 1,65 [12]). They identified three variables which had an important impact on the rising Pearl Index: to report Hispanic ethnicity, to have previously been pregnant, and to have rarely used effective hormonal contraception in the past [9]. In addition to these, Trussell and Portman concluded that changes in the

study population alone over time (e.g., with immigration, changes in marital status, contraception democratization) would decrease medication adherence [13•]. Gerlinger also noted a geographical difference between Europe and the USA, noting that the PI tends to be higher for the latter, but was unable to explain why [9]. Trussell and Portman in 2013, as well as Abascal in 2015, offered some explanation. The first two hypothesized that European women were more inclined to correctly and systematically adhere to their medication, whereas the US women who participated in different contraceptive trials tended to be uninsured women of low socioeconomic status, which was associated with weaker adherence [13•]. Abascal reported that for a 91-day extended-regimen COC containing 150 μg of levonorgestrel and 30 μg EE, the US study reported a PI of 1,34 and the European study a PI of 0,76. In this scenario, the US study included all the pregnancies that happened up to 14 days after the end of the study, unlike the European study that only included pregnancies occurring up to 2 days after the end of the study [14].

In addition to subject characteristics, study methodology can also explain a change in PI. Methods used to detect pregnancies and the definitions of pregnancies included in the Pearl Index calculation have changed over time. Traditionally, pregnancies were self-reported, whereas now testing is more rigorous, done routinely and using far more sensitive pregnancy tests. This allows for the detection of very early pregnancies that may have ended in spontaneous abortion [8•, 13•]. Moreover, including pregnancies due to the user's adherence failure versus that of the method's failure changes whether one calculates the actual efficacy of the medication or its effectiveness in real life [8•]. In addition, the definitions of user failure and method failure may also change from one study to another.

If the decrease in EE dose was responsible for a decrease in efficacy (perfect use), a similar decrease in effectiveness (typical use) would be expected. According to the National Survey of Family Growth (NSFG), the oral contraceptive failure rate was 2.0 % in 1973 (where the subjects were mainly married women), 8.8 % in 1995, and 8.7 % in 2002. The popularity of OCs with less than 35 μg of EE increased after 1995, when a decrease in the contraceptive effectiveness had already been observed [13•].

In light of all this, the Pearl Index must be considered with caution, especially since there are other tools to express contraceptive efficacy, such as life-table analysis. Life-table analysis, by estimating separate failure rates for each month, lets us calculate a cumulative failure rate for any period of exposure that excludes the time-related biases associated with the Pearl Index [8•, 13•]. In fact, the PIs tend to decrease with the length of the study because the probability to become pregnant diminishes over time [13•]. Women become more experienced in using contraception, diminishing risk of incorrect use, and women who are non-adherent or more fertile who become pregnant exit the study, leaving women who may be more adherent or less fertile to contribute to study results [8•].

Extended and Continuous COC Regimens

In an effort to improve contraceptive adherence, efficacy and side effect profile, not only has the EE dose decreased over time but pill scheduling has evolved.

COCs were initially provided on a 21/7 (21 days active pill/7 days placebo) schedule to imitate a woman's natural cycle. However, there is no biological reason to support having a withdrawal bleed each month [1]. For some women, it is preferable to avoid menstruation for medical reasons such as anemia, dysmenorrhea, premenstrual syndrome or dysphoric disorder or personal preference. COC regimens of 21/7 or 24/4 can be used in an extended or continuous form as well as some extended-cycle COCs of 84/7 [15].

A 2014 Cochrane review compared extended regimens (more than 28 consecutive days of active hormones) with traditional 21/7 or 24/4 regimens [15]. Authors evaluated satisfaction, adherence, rate of study discontinuation, rate of pregnancy, endometrial thickness, bleeding patterns, menstruation-associated symptoms and side effects. They analyzed 12 randomized controlled trials from 1993 to 2013. A meta-analysis was impossible because there were too many variations in the type of hormones used (mostly progestins), the doses (doses of EE varying from 20 to 50 μg in 49 to 365-day cycles), the delivery system (COC, vaginal ring or patch) and the length of each study (6 months to 1 year). Authors were nonetheless able to draw certain conclusions from their analysis. Among others, the outcomes for bleeding showed either no major difference between groups or less bleeding and/or spotting with extended or continuous-dosing COC [15]. Less bleeding did not translate into higher satisfaction or continuation in any study. However, less bleeding did translate into a significant improvement in menstrual-related symptoms, such as headaches, genital irritation, tiredness, bloating, and menstrual pain in many studies [15].

In general, there is more published experience with fixed extended COC regimens than with flexible regimens. One study included in the Cochrane review presented a flexible extended regimen of 120 days of EE (20 μg) and drospirenone (3 mg) [16]. The schedule is said to be flexible because women received the instruction to take a 4-day pause (tablet free) if 3 days of bleeding and/or spotting happened between days 24 to 120 of their cycle [16]. According to two RCTs conducted in 2012, when comparing the conventional fixed extended regimens with the flexible extended regimen, the latter allowed for a significantly lower number of bleeding and/or spotting days per year [12, 16, 17]. Women experienced less dysmenorrhea with this type of regimen [17]. Advice to women to avoid taking a pause in their COCs before the 25th day of their cycle allows for sustained ovarian suppression and

adequate contraceptive efficacy with Pearl Index's of 1,65 (in the Jensen, et al., study) and 0,74 (Klipping, et al., a 2-year study). There were no statistical or clinical differences in adverse events between the groups in either study [12, 16].

Several studies have shown that unscheduled bleeding happens more frequently between days 43 to 58 of extended cycle regimen, usually around the 49th day [18]. In order to diminish these irregularities, a potential strategy is to slowly increase the dose of estrogen over the cycle, to stabilize the endometrium, or to use a low-dose of EE instead of placebo to reduce follicular growth during the pause period [18]. One such formulation is an ascending-dose, extended-regimen COC that consists of a constant dose of levonorgestrel 150 mg on days 1 to 84, with EE 20 μg on days 1 to 42, 25 μg on days 43 to 63, 30 μg on days 64 to 84, and 10 μg of EE monotherapy on days 85 to 91 [19]. According to the phase III, open-label, multicenter study conducted in 2011 with 3597 women, days of unscheduled bleeding/spotting consistently decreased from cycle 1 to cycle 4 [18]. There are no comparison studies with a stable dose EE extended regimen.

The extended COC regimens, by decreasing withdrawal bleeding and hormone-free period, in addition to decreasing the symptoms of premenstrual syndrome and dysphoric disorder, dysmenorrhea and bloating, can also help reduce related costs (like absenteeism, feminine hygiene products, and consultations with the health care system) [20]. Different COC regimens offer different benefits, but it is paramount to individualize contraception counseling and take into account patient's preferences [20].

New Technologies to Improve oral Contraceptive Use

Many innovative strategies have been explored in the recent decade in order to improve oral contraceptive adherence, uptake, and continuation. These include 'mobile health' interventions such as use of mobile phone text messaging, phone calls, or smartphone applications. While data for contraceptive use is limited, such technologies have proven beneficial in other health contexts such as management of acute or chronic illness (diabetes, asthma), promotion of behavior change (smoking cessation), increased medication adherence, appointment attendance or delivery of patient test results [21–26].

Different types of interventions can be used alone or in combination with more traditional face-to-face contraceptive counseling. They can be one-way or two-way communications. Different communication strategies can be combined such as video transmission, voice mail, and text messaging [27, 28].

These strategies have potential advantages, which have been shown in other settings. They can reach people at any time and wherever they are. They allow young people familiar with these technologies to access health information. Additionally, they can reach rural populations and others that might otherwise not have easy access to care. Multifaceted interventions seem to be more effective to improve adherence than single-technology approaches. For example, mobile phone reminders alone to take medication have not shown any benefits. Based on evidence from other applications, the content of text messages should include health information, behavior change techniques, or content to increase motivation [25]. A potential risk associated with mobile phone interventions is traffic accidents, probably because of the distraction caused by texting while driving [29•]. Otherwise, such approaches are low-risk. Because of the sensitive and confidential nature of contraception, though, it is possible that phone sharing (with partner or parents) could be an obstacle, as could limited literacy or sporadic network coverage in low resource settings [29•]. A 2015 Cochrane systematic review analyzed five RCTs using different mobile phone strategies to either improve adherence or uptake of different contraceptive methods. Studies were too different in terms of intervention and outcomes to do a meta-analysis. Most were conducted in high resource settings (3 in the USA, 1 in Israel; the fifth was in Cambodia) [29•].

Three trials assessed adherence to a contraceptive method. Castaño, et al., (USA) sent different daily educational text messages for 180 days and saw higher self-reported continuation of pills at 6 months compared to standard care (RR1.19, 95 % CI 1.05 to 1.35). The effect did not seem to persist beyond 6 months, after the intervention was finished [30]. Hou, et al., in the USA, sent daily reminder text messages and recorded pill adherence with an electronic monitoring device (EMD) at each cycle for 3 months. The intervention did not improve pill taking and adherence was poor in both groups (mean difference (MD) 0.5 missed pills, 95 % CI −1.08 to 2.08) [31]. Trent, et al., in the USA sent daily text messages to adolescent users of Depo-Provera, including reminders of appointments (starting 72 h before their scheduled appointment) and healthy self management messages over the course of the enrollment period. The intervention group had a lower mean number of days between scheduled appointment and actual attendance for Depo-Provera injection for visit one only, not the subsequent visits (MD −8.60 days, 95 % CI −16.74 to −0.46) [32].

Two trials aimed to improve adherence as well as uptake. Smith, et al., in Cambodia, used six interactive voice messages, counselor-delivered phone support according to the response to messages and additional reminder messages for OC or injectable users after an abortion. Participants in the intervention group were more likely to report using effective contraception at 4 months post-abortion (relative risk (RR) 1.39, 95 % CI 1.17 to 1.66) and there was no increase in potential adverse events such as traffic accidents and domestic abuse [33]. And finally, Tsur, et al., in Israel found no difference in

self reported contraceptive use in a group of women taking isotretinoin for acne treatment randomized to either text messaging and e-mails vs. standard care at 3 months (RR 1.26, 95 % CI 0.84 to 1.89) [34].

These studies provide limited evidence that mobile phone interventions could increase contraceptive use especially on a short-term basis. The follow-up period never exceeded 12 months and there is lacking evidence of a long-term benefit. The theoretical background for the type of intervention chosen in each study was lacking in all studies and the cost-effectiveness of these strategies is still unknown [29•]. Larger well-designed trials might answer these questions and measure pregnancy and abortion outcomes. We also need to better understand what type of intervention gives better behavior change results. For now, mobile phone technology can be incorporated in a wider health service delivery strategy.

Oral Contraceptives Over the Counter (OTC)

Many contraceptive methods have been available for several years, but unintended pregnancies remain an important public health problem, accounting for about 50 % of all pregnancies in the USA [35]. Among other explanations, access to contraception remains difficult for many women. Prescription-only access can be a barrier for some. Since 2012, the American College of Obstetricians and Gynecologists has recommended OTC access to OCs, after evaluating the risk-benefit ratio based on available data [35].

According to a 2013 US survey, more than 60 % of women were in favor of OTC access to COCs [36]. Another US survey, in 2004, revealed that 41 % of women who did not use any method of contraception would be willing to start one (pill, vaginal ring, or patch) if it were available directly at the pharmacy, without having to meet a physician first [37]. OTC availability of the pill could also improve continuation and compliance [35]. One RCT has shown that providing multiple packs of pills at one time increases continuation at 6 months [35]. Convenience and privacy are two major benefits of this approach [38].

Doctors, pharmacists, and women alike have raised concerns about safety of OTC access, especially for new users [38]. The general safety of COCs is well established [35, 36], but screening for contraindications often remains a concern. Several studies have shown that women can self-screen for contraindications [35, 37]. Furthermore, in 2008, a UK study suggested that women who accessed OTC contraception were in fact very careful about making sure they do not have contraindications [35]. All contraindications except for hypertension are based on history and require no clinical judgment or further investigation [37]. Another concern is cervical cancer and sexually transmitted diseases screening that could be missed if no medical visit is necessary to get contraception [35, 37, 38]. These tests are not medically required to prescribe contraception [35, 37], and linking them as such can create barriers to access.

Some stakeholders consider that working to bring COCs OTC is a waste of time and more focus and energy should be invested on promoting long-acting reversible contraception (LARC) with their higher efficacy [39•]. LARCs are certainly excellent methods of contraception, but providers should respect women's choices if they prefer pills, patches, or vaginal rings [2].

Cost of OTC OCs could also become an issue. Some insured women fear having to pay more if insurance does not cover contraception OTC [38]. Pharmacist's consultation fees as well as inappropriate refusal to provide OC might also add an extra burden. If OC are OTC, pharmacists will have to provide adequate counseling about pill use; a study of pharmacists in Canada indicated that was acceptable and feasible for them [40].

Conclusion

There have been some developments in oral contraception in the last decade, with decreased EE doses, different dosing regimens and schedules, and focus on strategies to improve adherence and access. Very low-dose EE pills show equivalent effectiveness to higher-dose pills (?) while potentially reducing side effects. Extended and flexible regimens seem to reduce irregular bleeding and menstrually associated symptoms. Use of mobile health technologies to increase adherence, uptake, or continuation of contraception show some promising results but long-term benefits and cost-effectiveness of these strategies are yet to be determined. Over the counter availability may increase access for many women.

There still remains an unmet need for contraception. Fear of side effects or adverse events, poor adherence, and barriers to access are still obstacles to start or continue the pill, which newer approaches have attempted to address. While highly effective, long acting reversible methods are being used by more and more women, there is still a demand for oral contraceptives around the world.

Compliance with Ethical Standards

Conflict of Interest Maude Côté-Leduc declares no conflict of interest.

Geneviève Roy declares personal fees and non-financial support from Bayer for work as a speaker, on advisory boards, and for conference travel expenses; she declares non-financial support from Actavis for conference travel and writing assistance; and personal fees from Merck for advisory board work. Dr. Roy is also a member of a family planning expert committee at the Quebec National Institute of Public Health.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Burkman R, Bell C, Serfaty D. The evolution of combined oral contraception: improving the risk-to-benefit ratio. Contraception. 2011;84:19–34.
2. Higgins JA. Celebration meets caution: long acting reversible contraception (LARC)'s boons, potential busts, and the benefits of a reproductive justice approach. Contraception. 2014;89(4):237–41.
3. ACOG practice bulletin no 110. Noncontraceptive uses of contraceptives. Obstet Gynecol. 2010;115(1):206.
4. Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 μg versus >20 μg estrogen combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013;8:CD003989.
5. Warner Chilcott Canada. Lolo monograph. Toronto: Warner Chilcott Canada; 2013. Website: http://www.actavis.ca/NR/rdonlyres/45C0D770-B17C-42B0-8DF4-729451E56DE6/0/131LoloPMFrDec202013Rev2.pdf (Consultation : september 2015)
6. FDA PI. Lo Loetrin Fe. 2012. Website : http://www.drugs.com/pro/lo-loestrin-fe.html%23i4i_clinical_studies_id_8a86f5a1-607e-4baa-a6b9-09ded3a75189 (Consultation : septembre 2015)
7. • Archer DF, Nakajima ST, Sawyer AT, et al. Norethindrone acetate 1.0 milligram and ethinyl estradiol 10 micrograms as an ultra-dose oral contraceptive. Obstet Gynecol. 2013;122(3):601–7. **This article constitutes the base of the analysis of the efficacy, safety and tolerability of very low-dose estrogen COC. It is, among other things, on the Pearl Index presented in this study that the questioning about the precision and the value of Pearl Index re-emerged, at least in Canada.**
8. • Burkman R, Clinical Pearls. Factors affecting reported contraceptive efficacy rates in clinical studies. Int J Fertil. 2002;47(4):153–61. **This paper provides multiple explanations of the discrepancy between Pearl Index between different studies and over time**.
9. Gerlinger C et al. Different pearl indices in studies of hormonal contraceptives in the United States: impact of study population. Contraception. 2014;90(2):142–6.
10. Bachman G, Sulak PJ, Sampson-Landers C, Benda N, Marr J. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. Contraception. 2004;70:191–8.
11. Nelson A, Parke S, Makalova D, Serrani M, Palacio S, Mellinger U. Efficacy and bleeding profile of a combined oral contraceptive containing oestradiol valerate/dienogest: a pooled analysis of three studies conducted in North America and Europe. Eur J Contracept Reprod Health Care. 2013;18(4):264–73.
12. Jensen JT, Garie SG, Trummer D, Elliesen J. Bleeding profile of a flexible extended regimen of ethinylestradiol/drospirenone in US women: an open-label, three-arm, active-controlled, multicenter study. Contraception. 2012;86(2):110–8.
13. • Trussell J, Portman D. The creeping pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills? Contraception. 2013;88:604–10. **This article suggests two factors that contribute mainly to the increase of Pearl Index over time : pregnancy tests that are used more often and that are more sensitive and a decrease in adherence of participants due to changes in demographics.**
14. Lobo Abascal P, Luzar-Stiffler V, Giljanovic S, Howard B, Weiss H, Trussell J. Differences in reporting pearl Indices in the United States and Europe: focus on a 91-day extended-regimen combined oral contraceptive with low-dose ethinyl estradiol supplementation. Europe J Contraception Reprod Health Care. 2015;2:1–4.
15. Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev. 2014;7:CD004695.
16. Klipping C, Duijkers I, Fortier MP, et al. Contraceptive efficacy and tolerability of ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomized, controlled study. J Family Planning Reprod Health Care. 2012;38:73–83.
17. Strowitzki T, Kirsch B, Elliesen J. Efficacy of ethinylestradiol 20 μg/drospirenone 3 mg in a flexible extended regimen in women with moderate-to-severe primary dysmenorrhoea: an open-label, multicentre, randomised, controlled study. J Family Planning Reprod Health Care. 2012;38:94–101.
18. Portman D, Kaunitz A, Howard B, Weiss H, Hsieh J, Ricciotti N. Efficacy and safety of an ascending-dose, extended-regimen levonorgestrel/ethinyl estradiol combined oral contraceptive. Contraception. 2014;89:299–306.
19. Darwish M, Bond M, Ricciotti N, Hsieh J, Fiedler-Kelly J, Grasela T. A comparison of the pharmacokinetic profile of an ascending-dose, extended-regimen combined oral contraceptive to those of other extended regimens. Reprod Sci. 2014;21(11):1401–10.
20. Mendoza N, Lobo P, Lertxundi R, Correa M, Gonzalez E, Salamanca A, et al. Extended regimens of combined hormonal contraception to reduce symptoms related to withdrawal bleeding and the hormone-free interval: a systematic review of randomised and observational studies. European J Contraception Reprod Health Care. 2014;9(5):321–39.
21. Neville R, Greene A, Mcleod J, Tracy A, Surie J. Mobile phone text messaging can help young people manage asthma [published erratum appears in BMJ 2008;336 (7649)]. BMJ. 2002;325:600.
22. FranklinVL WA, Pagliari C, Greene SA. A randomized controlled trial of sweet talk, a text-messaging system to support young people with diabetes. Diabet Med. 2006;23:1332–8.
23. Whittaker R, Borland R, Bullen C, Lin RB, McRobbie H, Rodgers A. Mobile phone-based interventions for smoking cessation. Cochrane Database of Systematic Reviews 2009, Issue 4. [DOI: 10.1002/14651858.CD006611.pub2]
24. Bastawrous A, Cheeseman R, Kumar A. iPhones for eye surgeons. Eye. 2012;26(3):343–54.
25. Free C, Phillips G, Watson L, Galli L, Felix L, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: a systematic review and meta-analysis. PLoS Med. 2013;10(1):e1001363. doi:10.1371/journal.pmed.1001363.
26. Free C, Phillips G, Galli L, Watson L, Felix L, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. PLoS Med. 2013;10(1):e1001362. doi:10.1371/journal.pmed.1001362.
27. Free C, Phillips G, Felix L, Galli L, Patel V, Edwards P. The effectiveness of M-health technologies for improving health and health services: a systematic review protocol. BMC Research Notes 2010;3(1):250. [: http://biomedcentral.com/ 1756–0500/3/250]
28. Kallander K, Tibenderana J, Akpogheneta O, Strachan D, Hill Z, Asbroek A, et al. Mobile health (mHealth) approaches and lessons for increased performance and retention of community health workers in low- and middleincome countries: a review. J Med Internet Res. 2013;15(1):e17.
29. • Smith C, Gold J, Ngo TD, Sumpter C, Free C. Mobile phone-based interventions for improving contraception use. Cochrane Database Syst Rev. 2015;6:CD011159. doi:10.1002/14651858.CD011159.pub2. **This recent systematic review provided a large overview**

on the question of new technologies used in contraceptive adherence.

30. Castano P, Bynum J, Andres R, Lara M, Westhoff C. Effect of daily text messages on oral contraceptive continuation: a randomised controlled trial. Obstet Gynecol. 2012;119(1):14–20. doi:10.1097/AOG.0b013e31823d4167.
31. Hou M, Hurwitz S, Kavanagh E, Fortin J, Goldberg A. Using daily text-message reminders to improve adherence with oral contraceptives: a randomized controlled trial. Obstet Gynecol. 2010;116(3):633–40. doi:10.1097/AOG.0b013e3181eb6b0f.
32. Trent M, Tomaszewski K. Family planning appointment attendance among urban youth: results from the depotext trial. J Adolesc Health. 2013;52(2):S88. doi:10.1016/j.jadohealth.2012.10.207.
33. Smith C, Ngo T, Gold J, Vannak U, Ly S, Free C. Mobile Technology for Improved Family Planning (MOTIF): a single blind randomised trial of a mobile phone-based intervention to support post-abortion family planning.
34. Tsur L, Kozer E, Berkovitch M. The effect of drug consultation center guidance on contraceptive use among women using isotretinoin: a randomized, controlled study. J Women's Health. 2008;17(4):579–84. doi:10.1089/jwh.2007.0623.
35. Over-the-counter access to oral contraceptives. Committee Opinion No. 544. American college of obstetricians and gynecologists. Obstet Gynecol. 2012;120:1527–31.
36. Grossman D, Grindlay K, Li R, Potter JE, Trussell J, Blanchard K. Interest in over-the-counter access to oral contraceptives among women in the United States. Contraception. 2013;88(4):544–52.
37. Grossman D. Should the contraceptive pill be available without prescription? Yes. BMJ. 2008;337:a3044.
38. Baum S, Burns B and all. Perspectives among a diverse sample of women on the possibility of obtaining oral contraceptives over the counter: a qualitative study. Women's health issues. 2015 :1–6
39.• Jarvis S. Should the contraceptive pill be available without prescription? No. BM. 2008;337:a3056.
40. Norman WV, Soon JA, Panagiotoglou D, Albert A, Zed PJ. The acceptability of contraception task-sharing among pharmacists in Canada—the ACT-Pharm study. Contraception. 2015;92:55–61.