Maturitas 78 (2014) 45–50

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Classical and newly recognised non-contraceptive benefits of combined hormonal contraceptive use in women over 40

Nicolas Mendoza*, Rafael Sanchez-Borrego

University of Granada, Obstetric and Gynecologic, Maestro Montero, 21, Granada, Spain

ARTICLE INFO

Article history:
Received 18 February 2014
Received in revised form 24 February 2014
Accepted 28 February 2014

Keywords:
Menopause transition
Hormonal contraception
Combined hormonal contraception
Non-contraceptive benefits
Natural estrogens

ABSTRACT

Although age is the most crucial predictor of a woman's reproductive capacity, it is assumed that there is still a risk of pregnancy in menopause transition, as occasional spontaneous ovulation is possible. Moreover, age alone is not sufficient to contraindicate the use of any contraceptive method, whether hormonal or not. The use of new CHC in women over 40 has not only been associated with an improved safety profile but has also been associated with other non-contraceptive benefits or the consolidation of already-known benefits. The studies with new CHC have demonstrated that efficacy and safety do not differ from the corresponding parameters observed in younger women. Additionally, the new CHC offers specific and especially useful benefits for women over 40 in the treatment of menstrual disorders. Finally, interest is currently focused on the potential of early diagnosis and the prevention of cardiovascular disease and depression, both of which may be alleviated by the CHC.

Contents

1. Introduction

The menopausal transition is an indefinite period in a woman's life between the time that the first changes in the menstrual cycle occur and the year following the definitive cessation of menstruation [1]. Although age is the most crucial predictor of a woman's reproductive capacity, it is assumed that there is still a risk of pregnancy in perimenopause, as occasional spontaneous ovulation is possible. Moreover, age alone is not sufficient to contraindicate the use of any contraceptive method, whether hormonal or not [2].

Most reviews dedicated to combined hormonal contraception (CHC) during menopausal transition describe the indications for CHC use, the potential risks, and when/how to discontinue CHC

* Corresponding author. Tel.: +34 653673769.
E-mail address: nicomendoza@telefonica.net (N. Mendoza).

http://dx.doi.org/10.1016/j.maturitas.2014.02.017
0378-5122/

[3]. However, these reviews lack a discussion of the potential non-contraceptive benefits of CHC use among women over 40. While there is strong evidence demonstrating that CHC use is associated with reductions in menstrual bleeding, menstrual cramping, and gynaecological cancers in young women, data regarding CHC use among women over 40 are lacking.

The objective of this review is to determine whether the non-contraceptive benefits of CHC observed in other age groups can be extrapolated to women over 40, if there are other specific benefits for them who do not have the youngest and if new CHC methods are best suited to the needs and characteristics of women over 40.

1.1. Health problems in women over 40

The menopausal transition is accompanied by complex processes that result from the cessation of ovarian activity. Although various neuroendocrine changes in the menopausal transition have been described, the central biological event of this period is the phasing out of ovarian activity, both in the number of follicles and in the quality of oocytes. Consequently, menopausal transition is a period of low fertility that is characterised by anovulation and poor oocyte quality. The serum levels of follicle stimulating hormone (FSH), oestrogen and progesterone fluctuate around menopause, while the LH levels are maintained within the normal range. An increase in FSH not only stimulates ovarian folliculogenesis at an accelerated rate until the onset of menopause but also increases the risk of multiple pregnancies. The increased folliculogenesis causes a greater production of oestrogens, which may contribute to irregular bleeding and symptoms such as bloating and breast tenderness [4].

Furthermore, some gestational complications increase with maternal age (i.e., gestational diabetes, hypertension, growth restriction, placental pathology and prematurity). As a result, both the number of operative or instrumental deliveries and the perinatal and maternal mortality and morbidity are increased in women over 40. Consequently, reproductive counselling is necessary to inform women about the risks regarding conception that age confers [1,5].

In addition to irregular bleeding and the deterioration of ovarian function, many women also complain of hot flashes and other symptoms that have been described in post menopause (sleep disturbances, irritability, premenstrual syndrome, mood changes, skin changes, musculoskeletal disorders, balance disorders and vaginal dryness). Although menopause transition affects most women, it is estimated that quality of life is affected in a meaningful way in 20% of women [6].

Recently, the importance of ovarian function cessation in depression and cardiovascular disease (CVD) risk was assessed, and a bi-directional relationship between these two conditions seems to exist, with both of these conditions also associated with the possibility of menstrual cycle alteration. Various neuroendocrine mechanisms are involved in this process, although the link that unites these conditions is the ovarian dysfunction. From this perspective, women in the menopausal transition period experience greater mood changes, even more than during the subsequent period, which is when the CD risk increases [7].

2. Combined hormonal contraception over 40

2.1. Use of CHC in women over 40

In Spain, the use of CHC in women over the age of 40 is low (13.9% of women 40–44 years, and 5.6% of women over 45), well below the average of the population (21.6%) and lower than CHC use in the past [8], while the abortion rate has increased in these women in the last decade [9]. These reports indicated that the main reasons for non-compliance with CHC in women over 40 were a fear of cancer and possible CHC-related side effects.

2.2. On efficacy and the missed pill in women over 40

In terms of contraceptive efficacy, data extracted from articles involving women over 40 demonstrate more favourable efficacy given that fertility decreases significantly with age. Additionally, compliance is also improved because the majority of women over 40 have already used some contraceptive method or are familiar with the administration of CHC [2].

The decrease in fertility may present an advantage for the older woman over the younger woman in the case of missed or delayed CHC pill taking. However, two recent systematic reviews about missed and delayed CHC pills do not address the question of age [10,11]. When the particular endocrinology of the ovarian cycle in women over 40 is considered, with its higher basal levels of FSH and greater recruitment of follicles, we found no cause to modify the usual recommendations regardless of the woman's age [12].

2.3. It is necessary to monitor the use of CHC in women over 40?

In general, prior to the initiation of CHC, the performance of a medical history that aims to identify the facts that may contraindicate or do not favour CHC use is recommended, especially with regard to a personal and family history of thrombosis. When monitoring CHC, the consensus recommendation is for patient contact, if any, at three or six months from the start of the treatment to improve adherence, without a recommendation for specific periodic check-ups due to the use of contraceptives. For women over 40, the decision to discontinue CHC should be based on individualised contraceptive counselling, as there is no current evidence that confirms the time at which ovarian function ceases; moreover, fertility in women over 50 years of age is extremely low [13].

2.4. Risks of CHC in women over 40

Most of the evidence regarding the risks and benefits of CHC is derived from studies of oral CHC use in women younger than 35 years of age, results from which have been extended to older women and to other routes of administration (patch or vaginal ring). However, a Cochrane Database Systematic Review show that patch users had more side effects and ring users generally had fewer adverse events than oral CHC users [14]; and a recent cohort study show that vaginal ring use and oral CHC use were associated with a similar arterial or venous thrombotic (VT) risk during routine clinical use [15]. In the same way, the risks and benefits of CHC have been observed mostly in women younger than 35 years, but there appears to be consensus that age alone does not imply any limitation in the use of CHC [16].

Age is associated with an increased risk of venous thrombosis, which increases after age 39 among women using CHC pills. Epidemiological studies have reported an increase in myocardial infarctions, which are believed to be associated with a thrombotic mechanism rather than with the development of atherosclerotic plaques and an increase in cardiovascular mortality in users of the CHC pill who smoke and are over 35. A consensus panel suggested that CHCs should not be given to women over 35 who smoke more than 15 cigarettes per day, but they can be considered in women who smoke fewer than 15 cigarettes per day, even for those >35 years old who have an occasional cigarette, since the risks of pregnancy in this age group are greater than the risks associated with OC use [17]. However, we agree with those who consider that smoking above the age of 35 is a contraindication to the use of CHC [18]. The relationship between smoking, the use of oral CHC and CVD may be associated with high concentrations of intravascular plasma

fibrinogen and fibrin deposition and with the enhanced expression of tissue factor from monocytes. Also, CHC should be avoided in women over 40 with obesity, hypertension or migraine headaches, in which case could bee candidates for progestin-only contraception [19,20]. Anyway, for healthy non-smoking women, age is not an obstacle to the use of hormonal methods.

Although age by itself increases the risk of breast cancer, it is unclear whether this risk is increased with the use of CHC. However, the risk of suffering from breast cancer is greater in premenopausal women than in postmenopausal women of the same age, but again, there is no evidence that CHC increases this risk more at this age than at any other, so age is not considered enough to modify the patterns of the prescription of CHC [21]. Moreover, the latest report of the Oxford-Family Planning Association contraceptive study (Oxford-FPA) reveals that CHC use had no effect on non-reproductive cancers or on breast cancer [22].

In a recent review of the timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers, the effect of timing was limited to breast cancers diagnosed before age 40 (OR 1.40; 95% CI 1.14–1.70; $P = 0.001$). The risk of early-onset breast cancer increased by 11% with each additional year of pill use when such use was initiated prior to age 20 (OR 1.11; 95% CI 1.03–1.20; $P = 0.008$). No associated increase was observed for women diagnosed at or after the age of 40 (OR 0.97; 95% CI 0.79–1.20; $P = 0.81$) [23].

In relation to the thrombotic risk, the latest revision of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) did not issue a cause for concern or new reasons that alter the balance between the risks and benefits of CHC. This report established different risks depending on the progestagen and mentioned age as an isolated factor of thrombotic risk [24].

Regarding the type of progestin, the PRAC confirming the data observed in large series [25,26] and indicates that the VT risk is lowest with the CHCs containing levonorgestrel, norgestimate and Norethisterone (5 and 7 cases yearly per 10,000 women), and higher with etonogestrel and norelgestromin (6 and 12 cases) or gestodene, desogestrel, drospirenona (9 and 12 cases). For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs, but further studies are ongoing or planned. The risk of arterial thromboembolism is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen. On the other hand, most progestagen-only contraceptive methods do not increase VT risk significantly, and a considerable literature demonstrate the non-contraceptive health benefits of the levonorgestrel-releasing intrauterine system in women over 40 relate to disturbances of menstruation and related symptom (heavy menstrual bleeding, iron deficiency, pelvic pain and endometrial hyperplasia) [27].

However, these risks are independent of age, and at no point in the document did it state that the use of CHC must be restricted in women over 40 [24].

2.5. Classical non-contraceptive benefits of CHC

The articles that review CHC use during perimenopause frequently do not cite the potential non-contraceptive benefits [3]. While there is strong evidence showing that CHC use is associated with reductions in menstrual bleeding, menstrual cramping, and gynaecological cancers in young women, the data among women in menopausal transition are lacking. Indeed, the great majority of studies evaluating these benefits have been conducted in women younger than 40, commonly in women less than 35 years of age [28].

Altogether, CHC has been used successfully to treat menstrual disorders in women over 40. Some guidelines have even suggested that the use in healthy women without menstrual disorders may reduce gynaecological cancers, bone mass loss, and premenstrual syndrome [29], although there is insufficient evidence to recommend the use of CHC solely for the primary prevention of any of these conditions at any age [24]. Additionally, there is little controversy regarding the use of CHC among women over 40 due to the above-mentioned benefits; however, it is known that some gynaecological cancers increase with age, as does menstrual irregularity, and that both are reduced with CHC use [30]. Consequently, there is no apparent reason to not extend the benefits demonstrated in younger women to women over 40.

With regard to the prevention of bone resorption, the maintenance of bone mineral density (BMD) will occur with CHC use, primarily in hypo-oestrogenic women over 40. Any type of CHC has been proven to be effective for osteoporosis prevention, although this effectiveness does not exceed the benefits obtained with certain sports [31]. A systematic review of 6 randomised prospective studies performed in women over 40 demonstrated that the use of CHC reduces bone resorption and might significantly increase BMD, even at a low dose. In contrast with these data, cross-sectional studies evaluating BMD in perimenopausal women have failed to detect any significant difference between COC users (even current users) and nonusers [32]. Moreover, there is no evidence that COC use reduces the risk of fracture prior to menopause [33].

CHC has been shown to reduce dysphoric disorder and premenstrual syndrome, including in women over 40 [34,35], although these benefits are more evident with the use of extended and continuous regimens (see next section). In addition, CHC can also provide symptomatic relief for women over 40 complaining of hot flushes, vaginal dryness or insomnia associated with fluctuating oestrogen levels [36].

Classically, other non-contraceptive benefits in other conditions have been considered; however, some of these (acne, dysmenorrhoea, hyperandrogenism and endometriosis) are not very common at age 40 and beyond, and many of these conditions may arise at any age (myoma, pelvic inflammatory disease, rheumatoid arthritis, multiple sclerosis, asthma, etc.).

But above all, the main non-contraceptive benefit of the CHC in women over 40 is the reduction of maternal deaths, just by reducing the number of unintended pregnancies, the improve of perinatal outcomes and child survival, essentially by increase interpregnancy intervals [37].

2.6. Is there a CHC or a regimen that is best for the woman over 40?

2.6.1. Shorten or eliminate the hormone-free period

In women over 40, continuous or extended hormonal contraception regimens (CR/ER) have shown similar rates of efficacy, safety, and compliance compared to the standard 28-day regimen and may also improve the specific symptoms associated with the hormone-free period [38].

Women with premenstrual syndrome or menstrual symptoms during the hormone-free interval who used conventional regimens were shown to benefit from the use of CR/ER, according to the 7 RCTs that assessed these regimens in women over 40 [39–45]. In a retrospective study, contraceptive vaginal ring users also showed lower frequencies of migraine with aura related to menstruation [46].

It should be noted that studies that have assessed the degree of satisfaction of users of CR/ER were aimed primarily at the improvement or elimination of regular bleeding, and these results showed that female satisfaction was higher when the number of bleeding periods of any type decreased. Additionally, reducing menstruation is a strategy used to treat women with heavy menstrual bleeding (HMB), anaemia, and endometriosis. In the case of HMB, most studies have noted that the bleeding rate and the intensity of

bleeding were lower and that the amenorrhoea rate was higher in CR/ER users [38,39,43,44]. In fact, a guideline on continuous and extended use of CHC has recommended these regimens in women with HMB or blood dyscrasias [47].

The risk of endometrial cancer is reduced in CHC users, and there appears to be a residual protective effect after CHC discontinuation. It appears unlikely that CR/ER would alter this benefit, considering the results of endometrial biopsies [48,49].

2.6.2. CHC with natural estrogens for women over 40

More recently, newer CHC that incorporates natural estrogens (NE) instead of ethinyl-estradiol (EE) has been demonstrated to be highly effective, well tolerated, and associated with a high level of user satisfaction. These formulations also appear to improve certain parameters (haemostasis and metabolism), which makes them especially attractive to women over 40. NE has a lower impact on oestrogen-hepatic proteins, and is more readily metabolised by the liver than EE (the ethinyl group on which slows down that process). The structure increases the bioavailability of EE compared with NE, but may also contribute to an increased likelihood of oestrogen-related adverse events [50,51].

One of the new oral CHC combines estradiol valerate and dienogest (E2V/DNG) in a 26/2 regimen and has an indication in the treatment of HMB. Apart from those matters that have improved their safety, an interesting observation is that most of the volunteers in trials that have permitted the use of E2V/DNG for the treatment of HMB have been older than 40. For the first time, this will allow details of contraceptive efficacy, safety and effects on other symptoms to emerge from this group of women, data that have been unavailable with other CHC [52,53].

In this regard, the data that enabled the adoption of E2V/DNG as CHC and for HMB treatment were derived from studies performed in Europe, the USA and Canada, all of which followed the 26/2 regimen. Only two of these studies included women over 40, which can be examined together as a measurement of high contraceptive efficacy, especially in older women. The total number of reported pregnancies was 13 in 2175 volunteers who were exposed for more than 23,000 cycles, with only one pregnancy in a woman over 35 [54,55].

Additionally, most of the women presented with normal or low menses, with 4 days of bleeding on average, which tended to decrease with successive cycles, and with a drop-out rate of only 2.5% due to menstrual irregularity. As a result, these benefits apply not only to women with HMB but also to women who value a reduction in normal menstrual bleeding. Despite the absence of prospective studies that compare the new CHC with the LNG-IUD, the latest revision of the Guide to the National Institute for Health and Clinical Excellence of the United Kingdom (NICE) establishes that the LNG-IUD is the first treatment of choice for women with HMB who do not wish to become pregnant [54].

In these studies, headaches and pelvic pain associated with the hormone-free period were also less frequent with E2V/DNG. Additionally, a diary-based pilot study has indicated that the use of a pill containing E2V/DNG for six cycles has a positive effect in women with menstrually related migraine and suggests an association between dysmenorrhoea and COC use as a potential feature of refractory head pain [55].

Additionally, although considered a rare side effect, some women experience a decrease in sexual desire and sexual response associated with the use of CHC, which may also be considered a cause of abandonment. However, improvement as measured by the Female Sexual Function Index has been observed with E2V/DNG with regard to other CHC with EE/LNG in women up to 50 years of age [56]. In another study of women up to 48 years of age, E2V/DNG also improved the quality of their sex lives as measured by specific scales [57].

The metabolic and haemostatic profiles of the new CHC are more favourable than those observed with old CHC [58,59]. Currently, particular importance has been assigned to the relationship between SHBG and the risk of VT, not because this protein is directly related to coagulation or fibrinolysis, but rather because EE will stimulate SHBG synthesis, which suggests that this action is also accompanied by an increased production of proteins involved in haemostasis and blood pressure. In this regard, some authors consider the SHBG increase as an indirect marker of the thrombotic risk, a hypothesis that presents an advantage to CHC with NE [60], although a recent comparative study did not demonstrate differences in SHBG levels or resistance to activated protein C between CHC with or without NE [61].

With regard to the cardiovascular safety profile of E2V/DNG, one reported case of leg DVT subsequent to a sprained ankle occurred in a 40-year-old woman 9 days after completing treatment with E2V/DNG. Notably, this woman had initiated contraception with depot medroxyprogesterone acetate in the interim. In addition, there was a single case of myocardial infarction in this study, which occurred in a 47-year-old woman who was in violation of the exclusion criteria (smoker aged >30 years at study entry) [49].

Additionally, the superiority of E2V/DNG for the treatment of *hormone withdrawal-associated symptoms* (HWAS), including headache, pelvic pain and bloating, has been demonstrated in women up to 50 years in HARMONY I and II trials [62,63].

In conclusion, E2V/DNG appears to represent a new NE-containing CHC with advantages with respect to those containing EE, not only in the treatment of HMB but also for women who wish to experience lighter bleeding and for women who are comfortable with the idea of using an NE as well as women seeking to allay their concerns associated with the general use of hormones. E2V/DNG may also improve sexual dysfunction or migraine associated with menstruation or with the use of other ACH. Although the metabolic and haemostatic data appear favourable, confirmatory studies are needed.

Other CHC with NE has been formulated with 2.5 mg of nomegestrol acetate (NOMAC) and 1.5 mg of 17β-estradiol (E2) in a monophasic oral 24/4 regimen [64]. Two large, international, randomised controlled trials have been conducted in women aged 36–50 years without changes in contraceptive efficacy or side effect with age [65,66].

3. Future perspectives

CHC has been successfully used to treat menstrual disorders in women over 40. Some guidelines have also suggested that the use of CHC in healthy women over 40 without menstrual disorders may reduce gynaecological cancers, bone mass loss, and menstrual symptoms. Recently, the importance of ovarian function cessation in depression and cardiovascular risk was assessed, and a bi-directional relationship between these two conditions appears to exist, with both of these conditions also associated with the possibility of menstrual cycle alteration. Various neuroendocrine mechanisms are involved in this process, although the link that unites these conditions is the ovarian dysfunction. In this sense, CHC may reduce levels of depressive symptoms among young women [67]. Therefore, women in the menopausal transition period experience greater mood changes, even more than during the subsequent postmenopausal period, which is when the cardiovascular risk increases [7].

Similar to what was proposed for menopause hormone treatment (HT), where a “window of opportunity” exists during which the cardiovascular effects of HT outweigh the risks [68], a “window of vulnerability” for cardiovascular disease and depression during perimenopause might also exist [69]. Could the new CHC mitigate

these risks and be considered as protective during this window of vulnerability? The new CHC has been associated with superior haemostatic and metabolic profiles. Indeed, current studies have recently begun to demonstrate positive results in postmenopausal women (ELITE, KEEPS, etc.). However, the effects of any CHC on cardiovascular parameters require further study, as strategies once believed to reduce disease risk have been shown to increase this risk if the hormone type, dose, or timing was not appropriate, as in the lessons learned from HT. As a result, further studies are required to investigate these and other possible beneficial effects of CHC in women over 40.

In addition to therapeutic value, a recent review suggests that CHC are cost-effective medications for many medical disorders in women (premenstrual tension, dysmenorrhoea, and menstrual bleeding) [70]. However, at present, we have insufficient data to determine whether any specific CHC or regimen is more efficient than any other at preventing such costs.

4. Conclusions

The main conclusion of this review is the reinforcement of the prevailing concept in nearly all guidelines regarding contraception: age is not a factor that contraindicates the use of any contraceptive method. Therefore, the choice of a contraceptive method for a woman over 40 should only be informed by her state of health, her life habits and her previous experience with other methods.

Regarding CHC, certain potential risks also increase with age, predominantly VT; however, according to published data, the incidence of VT in CHC users over 40 does not differ from that observed in younger women. Nevertheless, this claim must be interpreted with caution because most of the RCTs that have analysed the efficacy and safety of CHC included predominantly women younger than 35 years of age, and only rarely have they included volunteers older than 40.

The use of new CHC has not only been associated with an improved safety profile but has also been associated with other non-contraceptive benefits or the consolidation of already-known benefits. Interestingly, some RCTs with the new CHC have been conducted primarily in women over 40. These studies have demonstrated that efficacy and safety do not differ from the corresponding parameters observed in younger women. Additionally, the new CHC offers specific and especially useful benefits for women over 40 in the treatment of menstrual disorders. Finally, interest is currently focused on the potential of early diagnosis and the prevention of CVD and depression, both of which may be alleviated by the new CHC.

Contributors

Nicolas Mendoza and Rafael Sanchez-Borrego: conception and design of the idea, data interpretation and preparation of manuscript.

Competing interest

None.

Funding

No one is on speaker's bureaus, received research funding or consulting. There was no funding source and no editorial assistance for this position statement.

Provenance and peer review

Commissioned and externally peer reviewed.

References

[1] Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertil Steril 2001;76:874–8.
[2] Mendoza N, Sanchez-Borrego R, Cancelo, et al. Position of the Spanish Menopause Society regarding the management of perimenopause. Maturitas 2013;74:283–90.
[3] Baldwin MK, Jensen JT. Contraception during the perimenopause. Maturitas 2013;76:235–42.
[4] Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159–68.
[5] Loane M, Dolk H, Morris JK. EUROCAT Working Group: maternal age-specific risk of non-chromosomal anomalies. BJOG 2009;116:1111–9.
[6] Avis NE, Colvin A, Bromberger JT, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: Study of Women's Health Across the Nation (SWAN). Menopause 2009;16:860–9.
[7] Bleil ME, Bromberger JT, Latham MD, et al. Disruptions in ovarian function are related to depression and cardiometabolic risk during premenopause. Menopause 2013;20:631–9.
[8] Los numerosos, bien-establecidos beneficios del noncontraceptive asociados con OC usan incluya las reducciones en los dos las condiciones ciclo-relacionadas (el eg, ciclos irregulares reducidos, el dysmenorrhea, el menorrhagia, la anemia, los quistes ováricos funcionales) y cánceres (el eg, ovárico, el endometrial, colorectal).Sánchez Borrego R, Martínez Pérez O, editors. Guía práctica en Anticoncepción Oral. Basada en la evidencia. Madrid: Emisa; 2003.
[9] http://www.msssi.gob.es/profesionales
[10] Zapata LB, Steenland MW, Brahmi D, Marchbanks PA, Curtis KM. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review. Contraception 2013;87:685–700.
[11] Zapata LB, Steenland MW, Brahmi D, Marchbanks PA, Curtis KM. Patient understanding of oral contraceptive pill instructions related to missed pills: a systematic review. Contraception 2013;87:674–84.
[12] Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.
[13] Lete I, Bermejo R, Parrilla JJ, et al. Use of contraceptive methods and risk of unwanted pregnancy in Spanish women aged 40–50 years: results of a survey conducted in Spain. Eur J Contracept Reprod Health Care 2007;12:46–50.
[14] Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev 2013;4:CD003552.
[15] Dinger J, Möhner S, Heinemann K. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstet Gynecol 2013;122:800–8.
[16] Stephen G, Brechin S, Glasier A. Using formal consensus methods to adapt World Health Organization Medical Eligibility Criteria for contraceptive use. Contraception 2008;78:300–8.
[17] Schiff I, Bell WR, Davis V, et al. Oral contraceptives and smoking, current considerations: recommendations of a consensus panel. Am J Obstet Gynecol 1999;180:S383–4.
[18] Briggs PE, Praet CA, Humphreys SC, Zhao C. Impact of UK Medical Eligibility Criteria implementation on prescribing of combined hormonal contraceptives. J Fam Plann Reprod Health Care 2013;39:190–6.
[19] Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.
[20] Cochrane RA, Gebbie AE, Loudon JC. Contraception in obese older women. Maturitas 2012;71:240–7.
[21] Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141–51.
[22] Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study. Contraception 2013;88:678–83.
[23] Kotsopoulos J, Lubinski J, Moller P, et al. Hereditary Breast Cancer Clinical Study Group. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Breast Cancer Res Treat 2014;143:579–86.
[24] www.ema.europa.eu
[25] Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011;342:d2139.
[26] Wu CQ, Grandi SM, Filion KB, Abenhaim HA, Joseph L, Eisenberg MJ. Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review. BJOG 2013;120(7):801–10.
[27] Fraser IS. Added health benefits of the levonorgestrel contraceptive intrauterine system and other hormonal contraceptive delivery systems. Contraception 2013;87(3):273–9.

[28] Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol 2013;122:139–47.
[29] The ESHRE Capri Workshop Group. Non contraceptive health benefits of combined oral contraception. Hum Reprod Update 2005;11:513–25.
[30] Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev 2013;22:1931–43.
[31] Babatunde O, Forsyth J. Effects of lifestyle exercise on premenopausal bone health: a randomised controlled trial. J Bone Miner Metab 2013 [Epub ahead of print].
[32] Nappi C, Bifulco G, Tommaselli GA, Gargano V, Di Carlo C. Hormonal contraception and bone metabolism: a systematic review. Contraception 2012;86:606–21.
[33] Lopez LM, Chen M, Mullins S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Syst Rev 2012;8:CD009849.
[34] Freeman EW, Halbreich U, Grubb GS, et al. An overview of four studies of a continuous oral contraceptive (levonorgestrel 90 mcg/ethinyl estradiol 20 mcg) on premenstrual dysphoric disorder and premenstrual syndrome. Contraception 2012;85:437–45.
[35] Sadler C, Smith H, Hammond J, et al. Southampton Women's Survey Study Group. Lifestyle factors, hormonal contraception, and premenstrual symptoms: the United Kingdom Southampton Women's Survey. J Womens Health (Larchmt) 2010;19:391–6.
[36] Kaunitz AM, Clinical practice. Hormonal contraception in women of older reproductive age. N Engl J Med 2008;358:1262–70.
[37] Cleland J, Conde-Agudelo A, Peterson H, Ross J, Tsui A. Contraception and health. Lancet 2012;380:149–56.
[38] Edelman A, Gallo MF, Nichols MD, Jensen JT, Schulz KF, Grimes DA. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. Hum Reprod 2006;21:573–8.
[39] Edelman AB, Koontz SL, Nichols MD, Jensen JT. Continuous oral contraceptives: are bleeding patterns dependent on the hormones given? Obstet Gynecol 2006;107:657–65.
[40] Legro RS, Pauli JG, Kunselman AR, Meadows JW, Kesner JS, Zaino RJ, et al. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. J Clin Endocrinol Metab 2008;93:420–9.
[41] Sulak PJ, Smith V, Coffee A, Witt I, Kuehl AL, Kuehl TJ. Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: a randomized controlled trial. Obstet Gynecol 2008;112:563–71.
[42] Teichmann A, Apter D, Emerich J, Greven K, Klasa-Mazurkiewicz D, Melis GB, et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. Contraception 2009;80:504–11.
[43] Rad M, Kluft C, de Kam ML, et al. Metabolic profile of a continuous versus a cyclic low-dose combined oral contraceptive after one year of use. Eur J Contracept Reprod Health Care 2011;16:85–94.
[44] Jensen JT, Garie SN, 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;86:110–8.
[45] Stephenson J, Shawe J, Panicker S, et al. Randomized trial of the effect of tailored versus standard use of the combined oral contraceptive pill on continuation rates at 1 year. Contraception 2013;88:523–31.
[46] Calhoun A, Ford S, Pruitt A. The impact of extended-cycle vaginal ring contraception on migraine aura: a retrospective case series. Headache 2012;52:1246–53.
[47] Guilbert E, Boroditsky R, Black A, et al. Society of Obstetricians and Gynaecologists of Canada. Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception, 2007. J Obstet Gynaecol Can 2007;29:S1–32.
[48] Anderson FD, Feldman R, Reape K. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. Contraception 2008;77:91–6.
[49] Kroll R, Reape KZ, Margolis M. The efficacy and safety of a low-dose, 91-day, extended-regimen oral contraceptive with continuous ethinyl estradiol. Contraception 2010;81:41–8.
[50] De Leo V, Fruzzetti F, Musacchio MC, Scolaro V, Di Sabatino A, Morgante G. Effect of a new oral contraceptive with estradiol valerate/dienogest on carbohydrate metabolism. Contraception 2013;88:364–8.
[51] Burke A. Nomegestrol acetate-17b-estradiol for oral contraception. Patient Prefer Adherence 2013;7:607–19.
[52] Palacios S, Wildt L, Parke S, et al. Efficacy and safety of a novel oral contraceptive based on oestradiol (oestradiol valerate/dienogest): a Phase III trial. Eur J Obstet Gynecol Reprod Biol 2010;149:57–62.
[53] Ahrendt HJ, Makalova D, Parke S, et al. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. Contraception 2009;80:436–44.
[54] National Collaborating Centre for Women's and Children's Health (UK). Heavy menstrual, bleeding. London: RCOG Press; 2007. NICE Clinical Guidelines, No. 44, http://www.ncbi.nlm.nih.gov/books/NBK56536/
[55] Nappi RE, Terreno E, Sances G, et al. Effect of a contraceptive pill containing estradiol valerate and dienogest (E2V/DNG) in women with menstrually-related migraine (MRM). Contraception 2013;88:369–75.
[56] Davis SR, Bitzer J, Giraldi A, et al. Change to either a nonandrogenic or androgenic progestin-containing oral contraceptive preparation is associated with improved sexual function in women with oral contraceptive-associated sexual dysfunction. J Sex Med 2013;10:3069–79.
[57] Caruso S, Agnello C, Romano M, et al. Preliminary study on the effect of four-phasic estradiol valerate and dienogest (E2V/DNG) oral contraceptive on the quality of sexual life. J Sex Med 2011;8:2841–50.
[58] Klipping C, Duijkers I, Parke S, et al. Hemostatic effects of a novel estradiol based oral contraceptive: an open label, randomized, crossover estudy of estradiol valerate/dienogest versus ethinylestradiol/levonogestrel. Drugs 2011;11:159–70.
[59] Junge W, Mellinger U, Parke S, Serrani M. Metabolic and haemostatic effects of estradiol valerate/dienogest, a novel oral contraceptive: a randomized, open-label, single-centre study. Clin Drug Investig 2011;31:573–84.
[60] Tchaikovski SN, Rosing J. Mechanisms of estrogen-induced venous thromboembolism. Thromb Res 2010;126:5–11.
[61] Raps M, Rosendaal F, Ballieux B, et al. Resistance to APC and SHBG levels during use of a four-phasic oral contraceptive containing dienogest and estradiol valerate: a randomized controlled trial. J Thromb Haemost 2013;11:855–61.
[62] Jensen JT, Parke S, Mellinger U, Serrani M, Mabey Jr RG. Hormone withdrawal-associated symptoms: comparison of oestradiol valerate/dienogest versus ethinylestradiol/norgestimate. Eur J Contracept Reprod Health Care 2013;18:274–83.
[63] Macìas G, Merki-Feld GS, Parke S, Mellinger U, Serrani M. Effects of a combined oral contraceptive containing oestradiol valerate/dienogest on hormone withdrawal-associated symptoms: results from the multicentre, randomised, double-blind, active-controlled HARMONY II study. J Obstet Gynaecol 2013;33:591–6.
[64] Mueck AO, Sitruk-Ware R. Nomegestrol acetate, a novel progestogen for oral contraception. Steroids 2011;76:531–9.
[65] Westhoff C, Kaunitz AM, Korver T, et al. Efficacy, safety, and tolerability of a monophasic oral contraceptive containing nomegestrol acetate and 17β-estradiol: a randomized controlled trial. Obstet Gynecol 2012;119:989–99.
[66] Mansour D, Verhoeven C, Sommer W, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. Eur J Contracept Reprod Health Care 2011;16:430–43.
[67] Keyes KM, Cheslack-Postava K, Westhoff C, et al. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. Am J Epidemiol 2013;178:1378–88.
[68] de Villiers TJ, Gass ML, Haines CJ, et al. Global Consensus Statement on menopausal hormone therapy. Maturitas 2013;74:391–2.
[69] Freeman EW. Associations of depression with the transition to menopause. Menopause 2010;17:823–7.
[70] British National Formulary, vol. 61. London, UK: Pharmaceutical Press; 2011.