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Long-Cycle Treatment with Oral Contraceptives

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Contents

Abstract

The conventional regimen of oral contraceptive (OC) use mimics the natural cycles by causing regular withdrawal bleeding, which can be avoided by omission of the hormone-free interval of 7 days. Consequently, long-cycle regimens with continuous administration of OCs for 3 or 6 months followed by a hormone-free interval of 7 days may reduce the frequency of menstruations and cycle-dependent complaints. Surveys have revealed that, despite a higher rate of irregular bleeding, the majority of women prefer the long-cycle regimen to the conventional OC regimen with regular bleeds every 4 weeks because it may improve quality of life.

As this regimen increases the contraceptive efficacy to a large degree, continuous treatment with OCs may prevent unintended pregnancies in women who miss a pill or are concomitantly treated with drugs that are able to impair the efficacy of OCs. Postponement of withdrawal bleeding may also reduce or prevent menses-associated disorders such as hypermenorrhoea and dysmenorrhoea, and have beneficial effects in patients with haemorrhagic diathesis, endometriosis, uterine leiomyoma and polycystic ovary syndrome. Continuous use of OCs prevents the cyclic fluctuations of serum levels of ethinylestradiol and progestogen and, hence, the cyclic variations of metabolic serum parameters.

Although the long-cycle regimen is initially associated with an elevated rate of irregular bleeding, the total number of bleeding days that require sanitary product protection is lower than during conventional OC treatment. Many physicians tend to prescribe extended OC cycles for postponement of menstruation or reduction of frequency of regular bleeding.

This review summarises and examines the available data on OC long-cycle regimens. The data suggest that the rate of treatment-related side effects with OCs according to the long-cycle regimen is similar to that of conventional OC regimens. However, clinical trials are necessary to assess the impact of long-term OC long cycles on safety, particularly the risk of cancer and cardiovascular disease, and fertility after discontinuation of treatment.

Until the end of the 19th century it was widely believed that regular bleeding cleansed the body from accumulated 'poisons' and "serves as a venue for the excretion of morbid and sometimes malignant humour, whose retention never fails to be extremely injurious".[1] Today, long-term oligomenorrhoea is known to be associated with an increased risk of endometrial cancer due to a long-term unopposed exposure to endogenous estrogens.

On the other hand, until the beginning of the 20th century, menstrual bleeding occurred relatively less frequently compared with today, as women had an average of six livebirths or more, including a 3-year breast-feeding period. The modern woman has less than two children and can expect approximately 450 ovulations and menstruations, compared with 160 ovulations in women living 100 years ago.[2] This increased frequency of menstruations, which is associated with large hormonal fluctuations, is thought to be partly responsible for the development of several illnesses, such as endometriosis, anaemia, uterine fibroids, ovarian cancer and premenstrual dysphoric disorders. In many women, the cycle-dependent rise or fall of estradiol and progesterone levels is associated with various complaints such as cramping, bloating, swelling, headaches and back pain, which can be reduced but not totally suppressed by treatment with oral contraceptives (OCs).[3]

The use of OCs represents an effective method of fertility control that not only prevents undesired pregnancies, but also provides regular menstrual periods and protection from endometrial cancer. The good cycle control is brought about by the well known regimen of 21 days of taking an estrogen/progestogen combination, followed by a hormone-free interval of 7 days. Between days 2 and 4 of this interval withdrawal bleeding occurs owing to the rapid decline of circulating contraceptive steroids.

This is a regimen that has been adapted to the natural pattern of spontaneous ovulatory cycles, which reflect fertility. In reality, the 'menstrual' cycles during OC use are artificial cycles and associated with reversible sterility, and there is no necessity for regular bleeding in women who do not want to become pregnant.

For many years, physicians have prescribed OCs or high-dose progestogens for postponement of

menstruation for medical reasons, for example dysmenorrhoea or excessive blood loss, but also to avoid inconvenience during leisure time, vacations or other social or occupational events.[4] It has also been common among sportswomen during training and competition. Long-cycle regimens are an example of medical applications commonly practised by physicians and patients before becoming the focus of clinical research. Before a prescription of long-cycle OC regimens is generally recommended, the available data on efficacy, adverse effects and risks must be considered. The present review summarises and evaluates the results of studies on extended OC cycles that have been published so far.

1. Acceptance of Long-Cycle Regimens

1.1 Attitudes of Women to Regular Menstruations

A survey carried out in The Netherlands revealed that the majority of women wished to have less frequent bleeding or amenorrhoea, concerning both spontaneous menstruations and withdrawal bleeding during treatment with OC or hormone replacement therapy. In the age group between 15 and 49 years, 55–60% of the women preferred withdrawal bleeding during OC use either every 3 months or never, while 30–35% wished to bleed monthly.[5] A study of Australian women revealed that 54% wished to have regular monthly bleeding, whereas 27% preferred withdrawal bleeding every 3 months and 15% preferred amenorrhoea during treatment with OCs.[6] Similarly, women in Scotland, China and South Africa did not like regular withdrawal bleeding during treatment with OCs.[7]

A representative survey carried out with 1195 German women of different age groups revealed that only 26–35% of the women preferred monthly bleeding, while 16–27% wished to bleed once every 3, 6 or 12 months, and 37–46% wished not to bleed.[8] The reasons for refusal of regular menstruations were fewer menstrual complaints, better hygiene, better quality of life and less blood loss. Many women would suppress menstruation sporadically for personal reasons.

It has been reported that the majority of patients on OCs who were still experiencing cycle-dependent complaints would prefer a regimen of extended active pills with a shortened hormone-free interval, in order to reduce frequency and severity of menses-associated symptoms.[9]

Among the women who preferred regular withdrawal bleeding during use of OCs, the main reasons were fear of pregnancy, infertility and adverse effects, and that menstruations are natural.[8] Regular withdrawal bleeding during the use of OCs mimics the normal ovulatory cycle and, therefore, reassures women of not being pregnant. Even though this bleeding is iatrogenic, some women regard it as a natural process that reflects fertility and health. If the menstruation is suppressed by continuous therapy, some women may fear that they have become infertile and are also anxious about pregnancy and side effects.

The uncertainty about the risks and objective benefits of long-term suppression of the menstrual cycle must be taken seriously, and potential negative psychological and sociological effects must be considered, particularly if OC-induced amenorrhoea is used as a lifestyle choice. On the other hand, beyond medical indications, the long-cycle regimen should be regarded as an option that allows the individual woman to choose the time and frequency of menstruations.

1.2 Current Clinical Practice of Gynaecologists Concerning Long-Cycle Regimens

The attitudes and experiences of physicians with the suppression of menstruation and long-cycle regimens of OCs were investigated by means of a survey of 9000 German gynaecologists. The response rate was 18% and 1152 questionnaires could be evaluated.[8] The results showed that nearly all physicians had experience with the postponement of menstruation by OCs and 97% had used a long-cycle regimen of OCs for a limited period of time. The reasons were medical indications (menstruation-related disorders or complaints, endometriosis, polycystic ovary syndrome [PCOS], increased contraceptive effi-

cacy) or request by the woman. The majority of the gynaecologists preferred a regimen of continuous use of three packs of OCs without hormone-free interval.[8] Regarding medical advice to patients, this might be a compromise to suppress bleeding only for a limited period of time, as no definite data on the long-term risks are available.

1.3 Cost Effectiveness of Long-Cycle Regimens

Calculations on the cost effectiveness of a trimonthly extended OC cycle revealed that it is cost effective when OCs are inexpensive and sanitary product usage is in the higher range because of menorrhagia. It is not cost effective when women tend to have low or average amounts of bleeding. As irregular bleeding decreases with duration of treatment, the cost of additional sanitary products is low.[10] In a trial comparing the bleeding frequency during treatment with either conventional 28-day cycles or extended 49-day cycles, the annual expenditure for hygiene products was significantly less for women on the long-cycle regimen.[11] An estimation considering the costs for OC prescriptions, hygiene products, pain relievers and physician visits for menstrual-related concerns, found that the long-cycle regimen appeared to be associated with societal and patient cost savings compared with conventional OC cycles.[12]

Beyond this, heavy or painful menstrual periods may have significant economic implications for working women, and the probability of work loss is 28% higher compared with women without abnormal menstrual bleeding. A reduction of these disorders by long-cycle regimens of OCs may lead to a considerable cost reduction.[13] Moreover, the cost of medical resources used for treatment of bleeding abnormalities, as well as their social impact, should be considered.

2. Contraceptive Efficacy

2.1 Timing of Missing the Pill

The conventional regimen of low-dose monophasic OCs (tablet taking for 21 days followed by a 7-day hormone-free interval) reliably prevents unintended pregnancies, provided that the tablets are taken according to the instructions. The proportion of women who conceive while taking the preparation without error is very low ('method failure'), and most of the unintended pregnancies are caused by missing tablets ('user failure'). It has been shown that compliance problems are common among all age groups, with as many as 47% of women missing one or more pills per cycle and 22% missing two or more pills per cycle.[14]

It has been demonstrated that missing pills immediately before or after the 7-day hormone-free interval puts women at the greatest risk of conception.[15] The extension of time without intake of the OC beyond 7 days increases the risk of pregnancy, whereas a shortening of the pill-free interval decreases it. The time of risk is at the end of the lengthened pill-free interval, either by delay of re-starting a new pack or by omission of tablets at the end of the previous pack.

The suppressive effect on gonadotropins exerted by OCs is time dependent and becomes maximal at the end of the treatment cycle. During the following 7 days without synthetic hormones, the negative feedback effect is abolished and the increasing gonadotropin levels cause ovarian follicular growth, as indicated by a rise of estradiol levels (table I).[16-22] This extends into the first treatment week and occurs more frequently during the use of low-dose OCs than with formulations containing ethinylestradiol 50μg.[17] Therefore, a delay of 2 days in re-starting the new pack after the 7-day pill-free interval is associated with an elevated risk of breakthrough ovulations, which sometimes occur as early as 9 or 10 days following the end of the previous pill cycle.[17] Ultrasound scanning of ovarian follicular activity has shown that, during treatment with low-dose OCs, a lot of women show maturation of follicles up to pre-ovulatory size, therefore maintaining the potential for ovulation.[23-25]

Table I. Mean serum concentrations of various hormonal parameters on days 6, 11, 21 and 28 of a control cycle and the third cycle of treatment with a triphasic oral contraceptive (OC) containing ethinylestradiol 30–40μg and levonorgestrel 50–150μg[22]

Parameter	Control cycle				Triphasic OC			
	day 6	day 11	day 21	day 28	day 6	day 11	day 21	day 28
LH (IU/L)	5.3	7.2	10.1	8.5	5.2	3.7	1.6	4.2
FSH (IU/L)	5.6	5.2	3.9	3.6	4.3	2.8	1.3	5.4
Estradiol (pg/mL)	50	95	141	86	17	18	16	35
Testosterone (ng/mL)	0.45	0.50	0.55	0.45	0.29	0.27	0.25	0.37
DHEA-S (ng/mL)	2394	2435	2547	2659	2134	2089	1703	1898
SHBG (nmol/L)	75	67	71	79	125	158	151	107
CBG (μg/mL)	45	44	45	42	84	90	89	71

CBG = corticosteroid-binding globulin; **DHEA-S** = dehydroepiandrosterone sulfate; **FSH** = follicle-stimulating hormone; **LH** = luteinising hormone; **SHBG** = sex hormone-binding globulin.

2.2 Effects of Shortening or Omitting the Hormone-Free Interval During Oral Contraceptive (OC) Use

In women using low-dose OCs, shortening of the hormone-free interval to 5 days has been shown to enhance the suppression of gonadotropins and to reduce the probability of re-establishment of follicular activity.[26] The lower the number of hormone-free days, the more pronounced is this effect. This could be demonstrated during the use of an ultra-low-dose OC with ethinylestradiol 15μg and gestodene 60μg after shortening of the hormone-free interval to 4 days.[27] Thus, the total omission of hormone-free days between two OC packs is very likely to increase the contraceptive efficacy. Omission of the hormone-free interval is generally recommended when the women change from a high-dose OC to a low-dose one in order to reduce the risk of unintended pregnancies.

Among all studies on the long-cycle OC regimen published so far (table II),[8,9,11,28-41] the only pregnancy occurred in a randomised study on the effects of an extended regimen (84 days with OC, 7 days without OCs) with a combination of ethinylestradiol 30μg and levonorgestrel 150μg. The Pearl Index for the long-cycle regimen was 0.60, that of the conventional regimen 1.78.[28]

2.3 Contraceptive Efficacy of OCs During Concomitant Use of Drugs

Shortening of the pill-free interval to 4 days has previously been recommended for women with suspected malabsorption or for patients who are on long-term enzyme-inducing drugs.[15] It is well known that concomitant treatment with certain drugs can reduce the contraceptive efficacy of OCs. Two mechanisms may interfere with the activity of contraceptive steroids. Certain drugs, for example barbiturates or rifampicin (rifampin), may induce hepatic cytochrome P450 (CYP)-dependent enzymes that are involved in the metabolism of ethinylestradiol or progestogens. Consequently, the inactivation rate of the steroids may be enhanced and their serum levels may decrease. Certain antibacterials may interrupt the enterohepatic circulation of ethinylestradiol by destroying the intestinal flora that hydrolyses ethinylestradiol conjugates and allows reabsorption of free ethinylestradiol.[42-46]

There are not only large inter- and intraindividual variations in the serum levels of ethinylestradiol and the progestogen component,[47] but also large interindividual variations concerning the interaction of drugs. Therefore, a more or less pronounced reduction of the ethinylestradiol and/or the progestogen level may be observed in some women, while in other women this is not the case.[42,45] Consequently, the frequently recommended use of OCs with higher ethinylestradiol doses may cause an unnecessary impact on metabolism in some women, whereas in other women the dose is still insufficient for maintaining contraceptive efficacy. More than 90% of unintended pregnancies reported in England until 1985 occurred during the use of high-dose OCs.[48]

As the shortening of the hormone-free interval to 4 days caused a profound suppression of follicular

Table II. Studies on long-cycle regimens of oral contraceptives (OCs)

Study (year)	Study type	Outcome	Treatment[a]	Number of women (% withdrawals)	Number of continuous OC days	Number of cycles
Loudon et al.[29] (1977)	Uncontrolled	Bleeding, adverse effects	EE 50/LYN 2.5	196 (44)	84	4
Hamerlynck et al.[30] (1987)	Controlled	Bleeding	Tri-EE/LNG	34	41	1
			EE 30/LNG 150	37	42	
			EE 30/DG 150	29	42	
de Voogt[31] (1991)	Uncontrolled	Bleeding	EE 30/DG 150	116 (9)	42	1
Kornaat et al.[32] (1992)	Uncontrolled	Bleeding, adverse effects	EE 30/GSD 75	55 (2)	42	1
Cachrimanidou et al.[33] (1993)	Randomised, controlled	Bleeding, adverse effects	EE 30/DG 150	198 (42)	63	5
			EE 30/DG 150	96 (33)	21	13
Cachrimanidou et al.[34] (1994)	Randomised, controlled	Haemostasis, lipid metabolism, SHBG, CBG	EE 30/DG 150	20 (35)	63	5
			EE 30/DG 150	10 (30)	21	13
Kovacs et al.[35] (1994)	Uncontrolled	Bleeding, adverse effects	EE 30/LNG 150	203 (71)	84	4
Coutinho et al.[36] (1995)[b]	Controlled	Bleeding, adverse effects	EE 50/LNG 250	446 (14)	336	1
			EE 50/LNG 250 vaginally	454 (14)	21	13
Ruchhoft et al.[37] (1996)	Randomised, controlled	Polycystic ovary syndrome, hormone levels	EE 30/DG 150	6 (33)	84	1
			EE 30/DG 150	6 (0)	21	3
			GnRH agonist	4 (0)	28	3
Sulak et al.[38] (1997)	Experiences in practice	Therapy of hormone withdrawal symptoms	Various OCs	50 (26)	42–84	Variable
Miller and Notter[11] (2001)	Randomised, controlled	Bleeding, adverse effects	EE 30/LNG 300	46 (37)	42	6
			EE 30/LNG 300	44 (45)	21	12
Sulak et al.[9] (2002)	Experiences in practice	Therapy of hormone withdrawal symptoms	Various OCs	267 (36)	42–84	Variable
Vercellini et al.[39] (2002)	Randomised, controlled	Endometriosis-associated recurrent pelvic pain	EE 20/DG 150	45 (20)	168	1
			CPA 12.5mg	45 (13)	168	1
Kwiecin et al.[40] (2003)	Randomised, controlled	Bleeding, adverse effects	EE 20/LNG 100	16 (6)	168	1
			EE 20/LNG 100	16 (6)	21	6
Miller and Hughes[41] (2003)	Randomised, controlled	Bleeding	EE 20/LNG 100	39 (18)	336	1
			EE 20/LNG 100	40 (30)	21	12
Anderson and Hait[28] (2003)	Randomised, controlled	Efficacy, bleeding, adverse effects	EE 30/LNG 150	456 (41)	84	4
			EE 30/LNG 150	226 (29)	21	13
Wiegratz et al.[8] (2004)	Experiences in practice	Bleeding	EE 30/DNG 2	30 (0)	189	1

a Doses are given as µg, except those of LYN (2.5mg) and DNG (2mg).

b Tablets were administered intravaginally.

CBG = corticosteroid-binding globulin; **CPA** = cyproterone acetate; **DG** = desogestrel; **DNG** = dienogest; **EE** = ethinylestradiol; **GnRH** = gonadotrophin-releasing hormone; **GSD** = gestodene; **LNG** = levonorgestrel; **LYN** = lynestrenol; **SHBG** = sex hormone-binding globulin; **Tri-EE** = triphasic OC with EE and LNG.

maturation, even when an ultra-low-dose OC with only ethinylestradiol 15µg was used,[27] total omission of hormone-free intervals may be an option for patients on long-term therapy with drugs that are known to interfere with the efficacy of contraceptive steroids. The ethinylestradiol levels during treatment with the ultra-low-dose OCs are half those with OCs containing ethinylestradiol 30µg. As in the case of an enzyme induction by, for example, rifampicin, phenytoin or carbamazepine, the average reduction of the serum levels of ethinylestradiol and the progestogen does not exceed 50%,[49] a long-cycle regimen with an OC containing ethinylestradiol 30µg offers a sufficient contraceptive efficacy which is probably superior to the conventional use of high-dose preparations. Consequently, the continuous use of OCs without a hormone-free interval has been recommended for such patients instead of in-

creasing the daily ethinylestradiol dose in conventional OC cycles.[50] This regimen can also be recommended in women who are treated with drugs with a teratogenic potential such as isotretinoin, and who, therefore, need a very safe contraceptive method.

3. Therapeutic Use of the Long-Cycle Regimen

3.1 Endometriosis

Endometriosis is associated with pelvic pain, dysmenorrhoea, dyspareunia and infertility. Growth of endometriotic lesions is estrogen-dependent and suppression of ovarian steroid production leads to the regression of the lesions. Endometriotic tissue is characterised by a deficient expression of 17β-hydroxysteroid dehydrogenase type 2 which converts estradiol to estrone but is not involved in the metabolism of ethinylestradiol.[51] Suppression of ovarian estrogen synthesis by OCs may reduce the local estrogenic impact, as the proliferative activity of ethinylestradiol is less than that of estradiol.[52] Continuous treatment for 6 months with a combination of ethinylestradiol 20μg and desogestrel 150μg in patients with recurrent pelvic pain after surgery for symptomatic endometriosis resulted in a significant reduction of dysmenorrhoea, nonmenstrual pain and dyspareunia, and an improvement of quality of life and sexual satisfaction. The effect was similar to that of therapy with cyproterone acetate 12.5 mg/day, and two-thirds of the patients were satisfied or very satisfied after treatment.[39] It has been suggested that endometriosis is suppressed during use of OCs but the symptoms may recur after discontinuation of treatment.[53] Therefore, the efficacy of continuous use or long-cycle regimens of OCs in patients with endometriosis needs to be investigated in long-term randomised prospective trials.

3.2 Uterine Leiomyoma

Most uterine leiomyomas are asymptomatic, but in a certain proportion of patients they may cause pain and menorrhagia and may impair fertility. Fibroid growth can be inhibited by the treatment with gonadotrophin-releasing hormone (GnRH) agonists or antagonists, androgens, antiestrogens or aromatase inhibitors which suppress either the synthesis or the action of estradiol. As estrogen deficiency may cause vasomotor complaints, loss of bone mass and other disorders, it has been recommended to limit the duration of therapy or to use an add-back hormone replacement therapy.[54] Current users of OCs were found to be at reduced risk of uterine leiomyoma confirmed by ultrasound or hysterectomy.[55] It was hypothesised that the use of OCs may mask the presence of uterine fibroids by reducing symptoms such as menorrhagia. In women with leiomyomas, treatment with OCs did not significantly change uterine size or volume, but decreased the duration of menstrual flow and increased haematocrit.[56]

OCs do not only suppress ovarian estrogen synthesis but also the levels of total and free androgens, which can be converted locally into estrogens by aromatase present in uterine fibroids.[57] In contrast with the mentioned therapies, no estrogen deficiency symptoms are expected during treatment with OCs. It may be speculated that continuous use of OCs may enhance the beneficial effect observed during conventional treatment of women with leiomyoma. However, prospective randomised trials are needed to investigate the efficacy and safety of the continuous use of OCs in patients with uterine leiomyomas.

3.3 Polycystic Ovary Syndrome

In women with PCOS, continuous treatment with a monophasic OC causes a more pronounced suppression of ovarian androgen production than with the standard regimen and, therefore, may have better therapeutic effects on androgenic disorders.[37] During conventional OC use, the reduced androgen synthesis may recur during the hormone-free interval (table I).[18,20,22]

In a small study of patients with PCOS, conventional treatment with a combination of ethinylestradiol 30μg plus desogestrel 150μg resulted in a significant reduction of luteinising hormone (LH)

and testosterone, which was reversed during the hormone-free interval. In contrast, continuous treatment for 3 months without a 7-day break caused a profound, continuous suppression of LH and testosterone. This effect was comparable with that of monthly injections of a depot GnRH agonist.[37]

Even though OCs are the traditional therapy for the long-term treatment of PCOS and exert many beneficial effects, there are not sufficient data concerning health risks. As PCOS is associated with various risk factors for cardiovascular disease, a deleterious effect of OCs cannot be excluded.[58,59] This issue is controversial and studies on the long-term metabolic effects of OCs in patients with PCOS are necessary, both for conventional and long-cycle regimens.

3.4 Haemorrhagic Diatheses

In patients with haemorrhagic diathesis associated with, for example, afibrinogenaemia, factor XII deficiency, von Willebrand's disease or factor IX deficiency, continuous treatment with OCs prevents heavy and prolonged menstruation and withdrawal bleeding. In a young woman with afibrinogenaemia, prolonged and excessive menstrual bleeding was stopped by continuous treatment with a combination of ethinylestradiol 30μg and levonorgestrel 150μg.[60]

Iron deficiency has been diagnosed in about 10% of young women and iron-deficiency anaemia in 2.2%, and the proportion of women with iron deficiency correlates with the intensity and duration of menstruation.[61] Both in women with iron deficiency and iron-deficiency anaemia, reduction of the frequency and intensity of menstruations or withdrawal bleeding may improve the clinical situation. Therefore, in patients with abnormal uterine bleeding the long-cycle OC regimen may be useful after exclusion of organic causes.[62]

3.5 Cycle-Dependent Complaints

Up to 30% of fertile women experience symptoms known as premenstrual syndrome, which arise in the luteal phase and disappear during the menstrual phase. The leading symptoms are breast tenderness, oedema, depressive mood and irritability. The results of an Icelandic study showed that treatment with OCs may improve cycle-dependent symptoms only to a small extent, if any.[63] Obviously, the changes in the serum levels of exogenous sex steroids may cause similar symptoms as the premenstrual fall of endogenous hormones in predisposed women. During treatment with OCs according to the standard regimen, hormone-related symptoms occur more frequently during the hormone-free intervals than during the 3 weeks on hormones. These symptoms include pelvic pain (70% in the hormone-free week vs 21% during tablet-taking), headache (70% vs 53%), bloating/swelling (58% vs 19%) and breast tenderness (38% vs 16%). In first-time users of OCs most of these symptoms are recorded more frequently but decrease during the first three cycles.[3]

It has been shown that monophasic OCs provide a stabilising effect on mood.[64] Consequently, a continuous, even influence of sex steroids might improve symptoms triggered by hormone withdrawal. In fact, an improvement of hormone withdrawal symptoms occurring during the conventional use of OCs has been reported by 74% of the women after switching to continuous treatment with low-dose monophasic OCs for 6–12 weeks.[3,38] The extended OC regimen was used for 5 years by nearly half of the women, and most of these had a reduction in the original cycle-dependent symptoms and a great improvement in their quality of life (table II).[3,38]

Migraine attacks occurring during the hormone-free interval under the conventional OC regimen may be caused by the decline of the ethinylestradiol levels.[65] Similarly, menstrual migraine in spontaneous cycles is suggested to be caused by the fall in estradiol before menses.[66,67] Two randomised studies comparing long-cycle regimens with conventional use of OCs revealed a significantly less occurrence of headache during treatment with extended OC cycles.[11,33]

3.6 Use of OCs in the Perimenopause

In the perimenopause, which is characterised by irregular cycles, treatment with OCs may stabilise the bleeding pattern and prevent endometrial hyper-

plasia. Surveys have confirmed that refusal of regular menses increases with age, and that up to two-thirds of women older than 50 years do not want to bleed at all.[8] This can be achieved by the continuous use of a monophasic combined OC without hormone-free intervals. Hypermenorrhoea, which occurs frequently in this age group, is reduced or prevented and, consequently, many diagnostic and therapeutic procedures, such as endometrial biopsies, hysteroscopy, pelvic ultrasonography or hysterectomy, can be avoided. The continuous hormonal influence may also decrease cycle-dependent psychological and physical complaints, and may prevent the accelerated loss of bone mass in women with estrogen deficiency.[68]

The use of OCs by fertile women is associated with no, or a slightly increased, risk of breast cancer.[69,70] This might be explained by the fact that exogenous sex steroids largely substitute the suppressed endogenous estrogens and progesterone. The situation may be different during the menopausal transition, which is mostly characterised by anovulatory cycles. Moreover, as the risk of cardiovascular disease increases with age, careful examination, screening and follow-up are necessary before and during the long-cycle OC regimen. Prospective trials are needed to assess the long-term risks.

4. Safety of Long-Cycle Regimens

4.1 Bleeding Pattern

The first study on the efficacy and acceptance of a long-cycle OC regimen was carried out as early as 1977.[29] This trial and subsequent studies using various ethinylestradiol/progestogen combinations (table II) observed an elevated rate of breakthrough bleeding and spotting at the beginning of the extended OC regimen. This improved during further treatment, and after a few long-cycles the incidence of irregular bleeding was similar to that in women treated with OCs according to the conventional regimen.[28,33,41]

The hitherto existing experience with long-cycle regimens shows that in the fourth and fifth week of continuous treatment the rate of irregular bleeding is elevated, particularly in women who were not pretreated with OCs. It seems as if the endometrium is accustomed to bleed regularly every 4 weeks and, therefore, is transitorily prone to irregular bleeding during that phase. This tendency disappears in most women during further treatment without hormone-free intervals. A detailed evaluation of the bleeding pattern recorded during an extended use of a combination of ethinylestradiol 30μg and dienogest 2mg revealed that the rate of bleeding was very low during the first 3 weeks of the extended regimen, but half of the women reported spotting while taking the second pack. Thereafter, the incidence of irregular bleeding declined to 10%.[8]

In most of the studies the number of bleeding days requiring protection was significantly lower during the extended use of OCs compared with that under the conventional regimen, whereas the number of spotting days was similar.[11,28,40,41]

The elevated incidence of irregular bleeding was more pronounced in first-time users of OCs compared with women who had used OCs according to the conventional regimen before starting an extended OC cycle.[8,33] The rate of irregular bleeding might be even lower in women who continue to use the same preparation after switching to a long-cycle OC regimen.[8]

It is reasonable to assume that triphasic OCs are less suitable for the long-cycle regimen than monophasic preparations, as shown in a comparative trial.[30] The large variations in the study design, duration of the long-cycle regimens, pre-treatment with OCs and the preparations used do not allow conclusions to be drawn on formulations which are most suitable for extension of OC cycles.

Similar to the oral use of ovulation inhibitors, the vaginal route of administration of a combination of ethinylestradiol with levonorgestrel seems to be suitable for an extended regimen.[36]

4.2 Endometrium

It is well known that the correct use of combined OCs reduces the incidence of endometrial hyperplasia and cancer by 50–60%, and the protective effect correlates with the duration of treatment.[71] It is not

necessary to induce regular withdrawal bleeding to prevent endometrial hyperplasia or cancer. As known from continuous-combined hormone replacement therapy that causes amenorrhoea, a continuous dosage of estrogen plus progestogen is more effective in preventing endometrial cancer than cyclic therapy, the latter being associated with regular withdrawal bleeding.[72] Continuous treatment with OCs, which causes a permanent and profound suppression of ovarian estrogen production, enhances the suppressive effect of the progestogen component on the endometrium. In a study of continuous treatment for 336 days with ethinylestradiol 20μg and levonorgestrel 100mg, the histological assessment of endometrial biopsies carried out in eight women revealed inactive or atrophic specimens in seven.[41]

4.3 Fertility

Although the profound suppression of ovarian function by OCs may lead to amenorrhoea in many women, there is no estrogen deficiency as the decline of estradiol is compensated for by the presence of exogenous ethinylestradiol. It has been shown that iatrogenic amenorrhoea is rapidly reversible, and follicular maturation begins soon after termination of the long-cycle regimen. The endometrium also responds to the rising levels of estradiol and progesterone, resulting in a normal menstruation. The available data suggest that there is no harmful effect of prolonged OC use on fertility after discontinuation.[73] However, further research on the impact of long-cycle regimens on fertility is needed.

4.4 Adverse Effects

Some of the studies on long-cycle regimens are characterised by a high withdrawal rate that may impair the evaluation of tolerability (table II). As the prevailing reason for discontinuation of treatment with OCs according to the extended regimen was irregular bleeding,[35] there might be differences according to the composition of the preparations. The results of clinical trials comparing the adverse effects of the conventional use of an OC with a long-cycle treatment with the same preparation generally revealed no difference in the rate and pattern of adverse effects, for example breast tenderness, nausea, nervousness, dizziness, acne, bodyweight changes and depression.[11,28,33,41] The only difference was the lower incidence of headaches during the long-cycle regimen compared with the conventional use of OCs.[11,28,33] This might be explained by the continuous influence of the estrogen component in those women who experience headaches in the hormone-free interval of the conventional regimen.

4.5 Long-Term Risks

Even though extended OC cycles have been prescribed by physicians individually for postponement of menstruation for many years, there are no data on the long-term risks associated with the long-cycle treatment with OCs. The hitherto existing experiences are insufficient, owing to the small number of trials carried out with a limited number of women for a short period of time. The longest published studies examining the effects of long-cycle regimens of OCs was for only one cycle of 336 days (446 women; 14% withdrawals) or four cycles of 84 days (456 women; 41% withdrawals) [table II].[28,36] According to the official guidelines,[74] studies on the effect of new OCs on surrogate parameters and safety should include at least 400 women completing 1 year of treatment. The risk of rare events cannot be evaluated in clinical studies because the number of women is too small. The risk of cancer or cardiovascular disease in young women can only be evaluated after treatment of a large number of women for a sufficient period of time.

It is not clear whether the prolongation of the influence of ethinylestradiol and synthetic progestogens by 1 week per cycle increases the relative risk of breast cancer and decreases that of endometrial and colon cancer compared with the standard regimen. The results of randomised studies on the effects of hormone replacement therapy suggest that the continuous use of estrogen/progestogen combinations by postmenopausal women is associated with a slight increase in the risk of breast cancer, whereas estrogens alone have a protective rather than a deleterious effect.[75,76] However, the interpretation of the results is difficult because the majority

of the women were obese and, therefore, had an elevated breast cancer risk. There are many observational studies on the effect of estrogens and estrogen/progestogen combinations on breast cancer risk in women with hormone deficiency, but the results are quite inconsistent and suggest no effect of estrogens only and a slight increase by estrogen/progestogen combinations.[77]

In fertile women, the situation is different as they have no hormone deficiency and the use of exogenous estrogen and progestogen largely substitutes the OC-induced suppression of endogenous sex steroids. Exogenous sex steroids have been shown to cause proliferation of mammary epithelium similar to that observed in the luteal phase.[78,79] However, in the monkey model, a combination of ethinylestradiol and norethisterone acetate did not cause such a proliferative effect.[80] Whether or not the prolongation of exogenous hormone exposure by 1 week per month increases breast cancer risk remains an open question. In the Million Women Study no difference in breast cancer risk was found between sequential and continuous estrogen/progestogen therapy.[81] On the other hand, the protective effect of OCs against benign breast disease correlates with the duration of treatment and the potency of the progestogen.[82]

The protective effect of OCs against ovarian cancer and endometrial cancer, which is dependent on the duration of treatment, may be enhanced rather than reduced during the use of extended OC cycles.

Another question is the relative risk of thromboembolic disease, which is increased 3- to 5-fold by the use of OCs.[83] It is highest during the first six treatment cycles, reflecting a role of predisposition, whereas the duration of treatment plays a minor role.[84] Therefore, a difference between the long-cycle regimen and the conventional use might be less pronounced. It is known that under the standard regimen of OCs various haemostasis parameters are changed at the beginning of tablet intake and are partly reversed during the hormone-free interval of 7 days. These fluctuations may reflect an imbalance between coagulation and fibrinolysis. However, on the other hand, continuous use may reach a steady state which might be at a significantly higher level than under the standard regimen. These effects will largely depend on the composition of the formulations. The introduction of long-cycle preparations will face the same problems as that of any new conventional OC: the change in surrogate parameters does not necessarily reflect the potential risks. Because of the fact that the absolute number of women with venous thromboembolic disease is very low in young women (1–2 per 10 000 women per year),[85] many thousand women-years of treatment will be necessary to look for differences in the risk elevation between conventional and long-cycle OC regimens.

It is well known that OCs cause a slight impairment of glucose tolerance and insulin resistance, but this is probably not relevant for the development of diabetes mellitus.[86] Whether the resulting slight hyperinsulinaemia can be regarded as a risk factor for arterial disease remains an open question.

5. Laboratory Parameters

5.1 Pharmacokinetics

Pharmacokinetic studies have shown that treatment with an OC increases serum ethinylestradiol levels during the first days of dose administration but, generally, a steady state is reached within the first 10 days of the treatment cycle, the peak serum level being 50–80% higher than on the first day.[47,87] A similar rise can also be observed with the progestogen levels, but there are large differences between the various compounds as regards binding to circulating sex hormone-binding globulin (SHBG) or a partial inhibition of inactivating CYP isoenzymes by the ethinyl group of nortestosterone derivatives.[47,87,88]

5.2 Metabolic Serum Parameters

There are only two studies that have compared the effect of conventional treatment with an OC for 12 months with that of an extended cycle regimen on lipid metabolism and haemostasis. Treatment with a combination of ethinylestradiol 30μg and desogestrel 150μg caused a rise in total cholesterol, total

Table III. Changes in various serum laboratory parameters after 1 year of treatment with an oral contraceptive containing ethinylestradiol 30μg and desogestrel 150μg, either according to the conventional (21 + 7 days) or the long-cycle regimen (63 + 7 days)[34]

Parameter	Conventional regimen (%)	Long-cycle regimen (%)	p-Value
Sex hormone-binding globulin	+240	+310	NS
Corticosteroid-binding globulin	+71	+191	NS
Total cholesterol	+8	+8	NS
Low-density lipoprotein cholesterol	−4	+20	NS
High-density lipoprotein cholesterol	+14	NC	NS
Total triglycerides	+44	+63	NS
Apolipoprotein A1	+37	+34	NS
Apolipoprotein B	+19	+25	NS
Fibrinogen	+3	+12	NS
Factor VII	+16	+31	NS
Antithrombin III	NC	NC	NS
Protein C	+7	+14	NS
Protein S	−10	−11	NS
Tissue plasminogen activator	−36	−41	NS
Plasminogen activator inhibitor	−50	−70	NS

NC = no significant change; **NS** = not significant; **p-value** = significant difference between both treatment groups.

triglycerides, and apolipoprotein A1 and B, but without any significant difference between the groups (table III).[34] In the same study, there was a significant increase in the levels of fibrinogen factor VII, thrombin-antithrombin complex and protein C activity, and a significant decrease of the tissue-plasminogen activator and plasminogen activator inhibitor (table III).[34] The changes in the coagulation and fibrinolysis parameters observed during the long-cycle regimen were comparable with those found under conventional treatment, even though the within-group alterations were somewhat more pronounced.[34] There was no significant difference in the levels of SHBG and corticosteroid-binding globulin, both of which increased largely after 3 months and remained at this level after 12 months.[34] The effect was slightly less in the conventional OC group, owing to the partial decrease of the serum globulin levels during the regular hormone-free intervals, as shown with a triphasic OC (table I).[22]

In a randomised 1-year trial on the effect of a combination of ethinylestradiol 30μg and levonorgestrel 150μg taken according to the conventional or a tri-monthly regimen, the changes in lipid parameters, for example the triglycerides or low-density lipoprotein-cholesterol, were similar.[28]

It is known that the metabolic effects of OCs depend largely on the composition of the OC, and the various metabolic serum parameters may increase or decrease. In the conventional regimen, these changes are mostly reversed during the hormone-free interval of 7 days.[89-91] Some parameters, for example the serum binding globulins, do not return to the baseline level within the 7 days without hormones (table I). Therefore, a further slight increase can be observed during the following cycles. However, in general, a steady state is reached within three cycles of conventional treatment with OCs.[89,91] It remains to be elucidated whether, and after what time period, a steady state is reached under continuous treatment or long-cycle regimens.

6. Conclusions

The use of OCs without hormone-free intervals profoundly suppresses the ovarian activity and increases the contraceptive efficacy. Therefore, during long-cycle regimens, the occasional omission of tablets is associated with a very low probability of an unintended pregnancy. Provided that the first pack had been taken correctly, forgetting up to seven consecutive tablets during continuous treatment will result in a pregnancy risk that is no higher than during the correct use of the conventional OC regi-

men. The long-cycle regimen is also the method of choice for patients who are concomitantly treated with drugs that may impair the efficacy of OCs.

Long-cycle regimens prevent symptoms caused by the fluctuations of estrogen and/or progestogen levels associated with ovulatory cycles or occurring at the beginning or end of a conventional OC cycle, for example headache and migraine.[92] The frequency and intensity of menstruations and, hence, menses-associated complaints is reduced. This regimen is also suitable for the treatment of dysmenorrhoea.

Many fertile women prefer amenorrhoea to regular menstrual periods. For these women the long-cycle regimen is a convenient and rapidly reversible method. Women can individually choose the time of withdrawal bleeding, which may be an advantage with respect to occupational requirements and leisure-time activities. Beyond the medical benefits, the extended use of OCs for a 3- or 6-month regimen has the potential of increasing patients' convenience and quality of life.

Moreover, heavy or painful menstrual periods may have significant economic implications for working women, and a reduction of these disturbances by long-cycle regimens of OCs may lead to a considerable cost reduction.

Theoretically, the increased number of days with hormones may increase health risks. However, both the desired and adverse effects depend primarily on the daily dose, which is the same as in conventional OC regimens or even lower. During the first days of daily administration of OCs, the serum concentrations of the contraceptive steroids increase, reaching a steady state within the first 2 weeks. In every hormone-free break of 7 days the changes in metabolic serum parameters observed during the active taking of OCs are at least partly reversed, and reach a steady state within several cycles. Under continuous treatment with OCs, the changes may reach a steady state earlier in the extended cycle, perhaps at a higher level, but this has to be investigated in controlled studies. It must be kept in mind that the ethinylestradiol-induced rise of many hepatic serum parameters (e.g. triglycerides, lipoproteins, haemostatic parameters, other serum proteins) is dose dependent and may be counteracted by the progestogen component, particularly those with androgenic activity. However, the clinical relevance of changes of such surrogate parameters remains an open question.

During a long-cycle regimen women do not have the marker of withdrawal bleeding to confirm contraceptive efficacy. Moreover, in the first months of treatment, irregular bleeding occurs more frequently than with the conventional regimen, particularly in first-time users of OCs. Even though the incidence of breakthrough bleeding and spotting (which are not predictable) declines with a longer duration of treatment, it may lead some women to discontinue the extended use of OCs.

Nevertheless, the available data demonstrate that the majority of women prefer the long-cycle regimen despite the higher rate of irregular bleeding, because the reduction of bleeding frequency and of complaints associated with cycle and menstruation improves quality of life.

However, there are no epidemiological data on the impact of long-cycle OC regimens on the fertility after discontinuation of treatment, the risk of cancer and cardiovascular disease.

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