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"The shorter, the better": a review of the evidence for a shorter contraception hormone-free interval

Alessandra Graziottin, MD

Director, Center of Gynecology and Medical Sexology, H. San Raffaele Resnati, Milan, Italy

President, Graziottin Foundation for the Cure and Care of Pain in Women

ABSTRACT

The menstrual cycle is characterised by cyclical fluctuations in oestrogens, progesterone and androgens. Changes in hormone levels in the pre-menstrual phase trigger a physiological local and systemic inflammatory reaction orchestrated by mast cells. This culminates in menstrual bleeding. When excessive and/or prolonged inflammation triggers systemic symptoms such as pelvic pain, headache, mood disorders and gastrointestinal discomfort in vulnerable women. In women taking hormonal contraceptives, menstrual bleeding is not biologically necessary and it may be advantageous to maintain more stable levels of oestrogens, progesterone and androgens throughout the cycle. New combined oral contraceptives (COCs) have been formulated with a progressively shorter hormone-free interval (HFI) (24/4 and 26/2) than traditional 21/7 pills, with the rationale of reducing hormone withdrawal-associated symptoms. A trend validated for both EE- and E2-containing contraceptive pills. Oestradiol valerate and dienogest (E_2V/DNG) is administered on the shortest 26/2 regimen. It has been shown to offer high contraceptive efficacy, together with a significant reduction in heavy menstrual bleeding, reduced anaemia and more physical and mental energy. Other benefits include reduction in hormone withdrawal-associated symptoms (headache and pelvic pain) and improvement in COC-associated sexual dysfunction. The shorter HFI also increases contraceptive efficacy. E_2V/DNG may therefore be a suitable alternative to conventional 21/7 COCs for women with bothersome COC- and menstruation-related symptoms with a higher contraceptive efficacy.

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INTRODUCTION

The biological reading of menstruation and associated symptoms is undergoing a new, intense scrutiny.[1-5] Traditionally, menstruation was considered the genital sign of the monthly renewal of the endometrium, triggered by the pre-menstrual fall in oestrogen and progesterone. Menstrual symptoms were considered 'psychosomatic,' their heterogeneity contributing more to a 'psychogenetic' reading than to a rigorous investigation of their common pathophysiology. The intensity of menstrual symptoms was thought to be modulated more by psychosocial factors than by biological ones. Only recently has the inflammatory basis of menstruation been systematically investigated.[1-6] In parallel, clear-cut evidence of the endocrine/inflammatory trigger of perimenstrual symptoms is emerging in the areas of dysmenorrhoea,[7,8] pelvic pain exacerbation and depression,[9,10] catamenial headache,[11] mood disorders and pre-menstrual symptoms[12] and Irritable Bowel Syndrome (IBS).[13]

Menstrual symptoms are complained of, although to a lesser degree, during the seven-day HFI.[14] Reducing the HFI to four[14–18] and, even better, to two days should reduce catamenial symptoms,[8,19–24] therefore improving women's physical and emotional wellbeing, their sexuality, and contraceptive efficacy. The aim of this paper is to review the evidence in support of this clinical hypothesis.

Menstruation: A historical perspective

Over the past 100 years there has been a marked change in what is considered normal with regards to menstruation (Figure 1). At the beginning of the 20th century, women experienced an estimated 140–160 periods in their lifetime. Today, they experience 450–480 periods − a threefold increase. Several factors have driven this change: an increasingly younger age at menarche, an older age at first pregnancy, a shorter duration of breastfeeding, fewer pregnancies overall and an older age at menopause.[25] Thus, current menstrual patterns, typified by monthly menstruation for decades on end, are not the historical norm. Indeed,

they may be considered to be new from the evolutionary point of view and unproven in terms of their health effects.

[Figure 1]

Menstrual bleeding is biologically necessary in some situations. If a woman is seeking to become pregnant, menstruation is needed to renew the endometrium so as to maintain optimal conditions for the blastocyst ahead of implantation. Menstrual bleeding may also be culturally necessary for some women, as a symbol of femininity. However, for women who are using hormonal methods of contraception, such as oral contraceptives (OCs), menstrual bleeding is not biologically necessary. Rather, women taking OCs need to have appropriate levels of oestrogens, progesterone and testosterone. Moreover, stable levels of oestradiol may confer improved wellbeing in comparison to fluctuating levels.[26] The more plausible reason is that fluctuations of oestradiol and progesterone trigger the mast cell's degranulation, contributing to a genital and systemic increase in inflammatory molecules and associated pain symptoms.

Systemic biological effects of menstrual bleeding

The physiology of the menstrual cycle is characterised by fluctuating levels of five key hormones: luteinising hormone (LH) and follicle-stimulating hormone (FSH), which are released by the anterior pituitary gland; and oestradiol, progesterone and testosterone, released by the ovaries. The perimenstrual phase, or luteal–follicular transition, is characterised by a decline in progesterone and oestradiol levels, as the corpus luteum regresses in the absence of pregnancy, followed by an increase in oestradiol levels during the post-menstrual phase (Figure 2).[27] The withdrawal of oestradiol and progesterone triggers mast cell degranulation at the basal layer of the endometrium, with local time- and intensity- limited inflammation, tissue breakdown and menstruation, as discussed in more detail in subsequent sections. Endometrial repair commences during menses and involves

resolution of inflammation, repair of damaged blood vessels and stroma and new tissue formation. Oestradiol is the dominant ovarian hormone in the proliferative phase and governs endometrial remodelling.

[Figure 2]

Menstruation as an inflammatory event

The molecular mechanisms by which oestradiol and progesterone exert control over the menstrual cycle involve interactions between the endocrine and immune systems.[1-6,27] In the immediate pre-menstrual phase, withdrawal of oestradiol and progesterone initiates a cascade of events (Figure 3) that includes the release of inflammatory molecules by mast cells and other immune cells. This induces a local and systemic increase of key inflammatory mediators (the chemokines interleukin-8 [IL-8] and matrix metalloprotease-1 [MMP-1]) and cyclo-oxygenase-2, the inducible enzyme responsible for synthesis of prostaglandins, as well as inhibition of prostaglandin dehydrogenase expression.[28,29]

These local events result in an increase in prostaglandin concentrations (PGE2 and PGF2a). There may be synergism with the chemokine IL-8. There is a consequential perimenstrual influx of leucocytes and macrophages, with a local increase in the number of other cells of haematopoietic origin such as mast cells.[1-6,27] These other cells produce and release cytokines that further augment leucocyte traffic. Together with endometrial stromal cells, they release enzymes such as MMPs, culminating in the breakdown of the extracellular matrix and initiation of menstruation.

[Figure 3]

The role of mast cells

Mast cells are considered to be the chief protagonists in the clinical scenario of inflammation and pain.[1-6,9,10,27] Mast cells are present in the endometrium and myometrium and are predominantly localised to the basal layer.[2] Pertinently for menstruation, mast cells are up-regulated in response to a wide range of stimuli, including neurogenic factors, fluctuating oestrogen levels and menstrual blood in the tissue.[10] Once activated, mast cells degranulate and release a diverse range of mediators, both pre-formed and synthesised *de novo*, which perpetuate the immune response.[2] Mast cell mediators in the human myometrium include histamine, serotonin, heparin, bradykinin, prostaglandin, tumour necrosis factor-alpha (TNF-alpha) and cytokines, including IL-4 and IL-6.[2]

Inflammation: physiologic versus pathologic

Menstrual inflammation is a necessary, physiologic process: it is a prerequisite for the renewal of the endometrium in non-pregnant women at every cycle.[1-6,27] When menstrual inflammation is physiologic (e.g., finalised or resolving) and limited in time and intensity, menstrual symptoms are mild/negligible or absent. When the local and systemic inflammation associated with periods is excessive and beyond the normal limits, in terms of intensity and/or duration, it may cause different symptoms of progressive severity. Leading symptoms are triggered by the effect of systemic and loco-regional inflammation: differences in type and intensity from one woman to another probably have a genetic basis, amplified by acquired and contextual factors. For example, the menstrual worsening of IBS symptoms in vulnerable women may be amplified by stressing events and/or dietary factors.[13]

[BOX]

Key point: Severe menstrual symptoms are the subjective and clinical correlate of a local and systemic inflammation beyond the physiological limits of intensity and/or duration. Reducing

menstrual inflammation is therefore strategic for reducing symptoms while improving women's quality of life during their fertile years.

[BOX ENDS]

Signs and symptoms of menstruation

Vaginal bleeding is the primary genital sign of menstruation. Periods can have different characteristics with different symptoms: heavy menstrual bleeding (HMB) is associated with increased menstrual pain (dysmenorrhoea) and iron deficiency anaemia (IDA). Pre- and/or post-menstrual spotting is frequently associated with irregular bleeding patterns. Symptoms around the time of menstruation may include abdominal bloating, abdominal cramps, fatigue, food cravings, headaches, mood swings, irritability and sore breasts. These are generally considered to be part of 'normal' menstruation. Other symptoms, less commonly considered yet also critical, include the perimenstrual worsening of asthma, allergies, joint and myalgic pain.

Dysmenorrhoea

Primary dysmenorrhoea, defined as pain associated with menstruation, is the most common menstrual disorder, estimated to affect at least half of women with different severity.[30] It is caused by uterine contractions associated with endometrial ischaemia and is associated with increased levels of inflammatory molecules, including prostaglandins, vasopressin, leukotriene and numerous mast cell mediators.[4,5,27,30]

The systemic symptoms of menstruation – such as fatigue, nausea, lack of energy, headache, diarrhoea, abdominal pain and cramps, mood swings and depression – are associated with increase of inflammatory molecules and dysmenorrhoea.[27] In a systematic review of risk factors for pelvic pain, both menorrhagia (heavy bleeding) and menometrorrhagia (irregular and heavy bleeding) were significantly associated with dysmenorrhoea,[31] indicating that dysmenorrhoea is a key feature of HMB.

HMB increases dysmenorrhoea from between two to five times.[31] It doubles the risk of endometriosis, a leading contributor to dysmenorrhoea and chronic pelvic pain. Contraceptive pills reduce dysmenorrhoea.[31] The pill containing oestradiol-valerate and dienogest, which is the main focus of this review, significantly reduces HMB (duration of periods and intensity of the bleeding) versus a competitor pill. It is the only pill approved for the treatment of HMB. The stable plasma levels of oestradiol, the effect of dienogest on the endometrium and the very short HFI (two days) all contribute to significantly reducing HMB and dysmenorrhoea.[8]

Chronic pelvic pain

Fluctuations in ovarian hormones are associated with worsening pain syndromes. The association is particularly strong for menstrual migraine and chronic pelvic pain.[32] Chronic pelvic pain may stem from different conditions including endometriosis, bladder pain syndrome, vulvodynia and IBS, which are often comorbid.[9,10] Pelvic inflammatory disease may further contribute. Central changes are often associated with this condition.[33] Pelvic and systemic inflammation is the common denominator of chronic pelvic pain, associated comorbidities, neuroinflammation and depression.[9,10] The pre-menstrual fall in oestrogen triggers and potentiates mast cell degranulation in the already inflamed organs and system, leading to a significant worsening of pelvic pain during both the natural cycle and the HFI of seven days.[14]

Menstrual migraine

In women who suffer from menstrual migraine/catamenial headache, the drop in circulating oestrogen levels that occurs 2–3 days before menstruation is believed to be partially responsible for the increase in migraine risk, likely mediated by mast cell degranulation in the dura mater and within the brain, in synergy with up-regulation of microglial cells with local release of inflammatory markers.[11,12,34]

Mood disorders

Many symptoms associated with menstruation are shown to have an inflammatory basis, potentiated by fluctuations in oestrogen. Inflammatory responses also have an important role in the pathophysiology of mood disorders, with depressed patients exhibiting higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules.[9,10,35] Women suffering from pre-menstrual depression show higher levels of inflammatory markers.[12] In common with the reduction in symptoms proven for other menstrual disorders, mood disorders are also likely to be reduced by stabilising oestradiol levels and reducing the HFI to two days.

Gastrointestinal symptoms

Inflammation of the bowel wall – with significant increase of mast cells, degranulated mast cells and, in particular, mast cells in close proximity to pain fibres – is the histologic correlate of IBS,[35] which was once considered to be just a 'psychogenic' pathology. Inflammatory pathways are also implicated in menstruation-related worsening of gastrointestinal symptoms.[13]

The gastrointestinal tract is the body's largest immune organ: it is richly innervated and contains mast cells, receptors for immune mediators and neuropeptide receptors. In women with IBS, the severity of symptoms – particularly in the somatic domains – fluctuates over the course of the menstrual cycle and tends to increase in the perimenstrual period (Figure 4).[13] Furthermore, compared with healthy controls, women with IBS report a significantly greater severity in cycle-associated gastrointestinal symptoms: cramps, abdominal bloating, diarrhoea and/or constipation.[13]

Mast cells are implicated in the pathophysiology of these observations: histological analysis of colon biopsies reveals a significant increase in mast cells and in activated (degranulating) mast cells in women with IBS versus controls, resulting in increased local levels of histamine

and tryptase. Furthermore, the number of activated mast cells in close proximity to colonic nerves is positively correlated with the severity of abdominal pain.[36]

[Figure 4]

Asthma and respiratory atopy

Asthma, allergies and other manifestations of atopy have also been shown to fluctuate throughout the menstrual cycle. Bronchial hyper-reactivity is more likely in the perimenstrual period than at other points in the cycle;[37] furthermore, an irregular menstrual cycle is associated with specific asthma phenotypes, namely atopic asthma and atopy.[38,39] One-third of acute respiratory distress in asthmatic women is precipitated during periods, leading to the so-called 'perimenstrual asthma' responsible for emergency admissions into hospitals. Understanding that the menstrual fall of oestradiol and progesterone triggers asthmatic crises in vulnerable women may suggest new preventive strategies, which are pathophysiologically oriented, such as stabilising hormone levels and reducing the HFI. Prospective controlled studies are needed to test this working hypothesis.

Advantages of providing stable hormone levels in place of monthly hormonal fluctuations

Whereas menstrual bleeding is necessary in women seeking to become pregnant, it is not biologically necessary in women taking hormonal contraceptives. Rather, for physical and mental good health, women require appropriate, stable levels of oestrogens, progesterone and androgens.

COCs – i.e. OCs containing an oestrogen and a progestogen – have traditionally been administered on a 28-day cycle, with 21 days of active treatment followed by a seven-day break (a '21/7' pattern) during which withdrawal (scheduled) bleeding occurs. Newer formulations are available in which the HFI is reduced or in some cases eliminated altogether.

There are three major rationales for a shorter HFI.

1. To provide more powerful ovarian suppression

The first rationale is that having a shorter HFI provides more powerful ovarian suppression. Studies have demonstrated that the conventional 21/7 regimen fails to induce complete ovarian suppression.[40,41] Consequently, the chance of ovulation during the HFI increases with each hormone-free day.[41]

From the contraceptive efficacy point of view, this also explains why missed doses at the start of the pill cycle are the least forgiving.

[Figure 5]

2. To reduce menstrual symptoms

A further rationale for shortening the HFI is to reduce genital and systemic inflammation and symptoms associated with hormone withdrawal, which can have a negative impact on women's wellbeing and quality of life. Similar to women who don't use hormonal contraceptives, menstrual symptoms in women taking COCs are more prevalent in the HFI, although with variable reduction in intensity in comparison with the average menstrual intensity reported in spontaneous cycles. In a study of nearly 300 women, pelvic pain, headache, breast tenderness, bloating/swelling and analgesic use were all significantly more frequent during the seven-day HFI than in the 21 days of active treatment (Figure 6).[14]

[Figure 6]

3. To reduce heavy menstrual bleeding

COCs with a shorter HFI have demonstrated clinically relevant benefits in women with menstruation-associated symptoms. HMB affects around one in three women and has a significant negative impact on all domains of health-related quality of life.[42] In a study of

adolescent girls, those with heavy menstrual bleeding reported significantly more severe symptoms of fatigue compared with controls.[43]

Evidence supporting the benefits of reducing the HFI

From 7 to 4 days

The shortening of the 7-day, pill-free interval (21/7) is probably one of the most important revolutions in terms of pill dosing advances.[17,44-46]

The first step was moving from 7 to 4 days (24/4). All of the 24/4 regimens, including EE/DSPR,[17] EE/Noretindrone acetate[45] and E2/NOMAC[18,47,48] have shown comparable or more favourable effects than 21/7 regimens in terms of efficacy and safety profiles.

Initial evidence suggests that the 24/4 regimens confer better cycle control with less breakthrough bleeding compared with 21/7 formulations containing 20 µg.[45] The shorter HFI of 4 days is also associated with greater and more consistent suppression of ovarian activity,[46] results in fewer unintended pregnancies,[17,45] and offers shorter episodes of withdrawal bleedings compared with a 7-day HFI.[49]

This translates into improved menstrual symptoms control − a critical advantage from the clinical point of view. Women's perception of a less symptomatic HFI, with increased general wellbeing (including feelings about their body) and higher energy perception translates into personal benefits far beyond contraceptive efficacy. These additional benefits have the potential to enhance compliance, adherence and consistency of use and should be specifically emphasised in the clinical consultation. The specific advantages of shortening the HFI from 7 to 4 days includes the significant reduction of PMS symptoms,[16,50] dysmenorrhoea,[16] pre-menstrual dysphoria disorder (PMDD)[51] and improvements in quality of life.[52]

Improvements on PMS symptoms and dysmenorrhoea

Results from a pooled analysis of two, one-year randomised studies comparing the effectiveness of 24/4 (E2/NOMAC) and 21/7 (EE/DRSP) in more than 3500 healthy women

showed that during both the pre-menstrual and menstrual phase, the estimated treatment difference significantly favoured the 24/4 pill for pain, water retention, negative affect and impaired concentration. Both regimens were beneficial in improving the cramps item score, however, this benefit was significantly greater for 24/4 E2/NOMAC than 21/7 EE/DRSP.[16]

Improvements in quality of life

In a retrospective study evaluating the acceptability of a COCs with a shortened HFI (3–4 days instead of 7 days), 82% of subjects reported an improvement in their quality of life, mainly related to improvements in menstrual-associated symptoms.[52]

From 7 to 2 days

The benefits of shortening the HFI may be even greater when further reducing it from 7 to 2 days. E_2V/DNG is a 26/2-pattern COC that features quadriphasic dosing, delivering a reducing dose of oestrogen over days 1–26 and an increasing dose of progestogen over days 3–24, followed by two hormone-free days. E_2V/DNG is the first COC approved for the treatment of heavy and/or prolonged menstrual bleeding due to endometrial dysfunction (i.e. without organic pathology). Benefits include:

Contraceptive efficacy

Contraceptive efficacy can be measured using the Pearl Index (the number of unintended pregnancies per 100 woman–years of exposure), which can be expressed in two ways. 'User and method failure' (also called the unadjusted Pearl Index) represents the failure rate with 'typical' use, whereas 'method failure' (also called the 'true pill failure' or the adjusted Pearl Index) represents the failure rate with 'perfect' (i.e. correct and consistent) use.

In clinical trials performed in the European Union and in North American, E_2V/DNG demonstrated very high contraceptive efficacy. In women aged 18–50, the unadjusted and adjusted Pearl Indices were 0.79 and 0.42, respectively. In a subgroup of women aged 18–35, the unadjusted and adjusted Pearl Indices were 1.01 and 0.51, respectively.[53] In a three-

cycle ovulation inhibition study, treatment with E_2V/DNG led to suppression of follicular development in the majority of women. Ovarian activity returned to pre-treatment levels during the post-treatment cycle.[53]

Reduction of HMB

E_2V/DNG significantly reduces the duration and severity of the menstrual bleeding and it is the only pill approved for the treatment of HMB. The efficacy of E_2V/DNG in women with heavy menstrual bleeding has been assessed in two randomised controlled trials.[54,55] In a pooled analysis of these studies, women who took E_2V/DNG showed an 88% relative reduction in median menstrual blood loss, from 142 ml to 17 ml, after six months.[56] The greatest reduction was achieved at the first withdrawal bleed after treatment initiation and it was sustained with no loss of effect throughout treatment (Figure 7).[56] In these studies, 29% of women taking E_2V/DNG were completely cured of all symptoms of dysfunctional bleeding at six months versus just 2% of women in the placebo group.[53] Besides menstrual blood loss, women were qualified as being cured of their symptoms only if they had responded to treatment, based on eight stringent criteria, including significant reductions in bleeding length, bleeding intensity and number of bleeding days. Furthermore, women using E_2V/DNG showed a significant improvement in iron metabolism parameters (haemoglobin, haematocrit and ferritin).[56]

[Figure 7]

Reduction of menstrual symptoms

Depression associated with HMB

HMB, and associated iron-deficiency anaemia, may also be a risk factor for depression: in a study of female students, low blood ferritin was significantly more frequent in women with depression than in their non-depressed counterparts.[57] Low iron levels have been shown to have a detrimental impact on the ability to concentrate, attention and memory.[58]

Furthermore, compared with healthy controls, young women with HMB showed higher fatigue severity scores and significantly higher menorrhagia severity scores.[43] In a sample of 48 women aged 11–17 with HMB, 87.5% had ferritin levels ≤40 ng/ml and 29.2% had ferritin levels ≤15 ng/ml.[43] Interestingly, in a study of 198 non-anaemic, iron-deficient, menstruating women with unexplained fatigue, iron supplementation was significantly more effective than placebo in improving fatigue.[59]

Menstrual migraine and pelvic pain

E_2V/DNG has also shown a reduction in systemic symptoms associated with the HFI such as headache. A prospective diary-based pilot study indicated that E_2V/DNG was associated with fewer migraine attacks, reduced duration and severity of headache and reduced use of analgesics compared with baseline.[23]

The Harmony I and Harmony II studies were designed to test whether it would be more advantageous for women affected by symptoms associated with the HFI to change from a pill containing ethinylestradiol plus norgestimate (EE/NGM) (Harmony I)[21] or ethinylestradiol plus LNG (EE/LNG; Harmony II)[22] with a 21/7 regimen to a pill containing E_2V/DNG with a 26/2 regimen. The aim of the two studies was to test the superiority of the 26/2 regimen against the 21/7 regimen, focusing on menstrual migraine and pelvic pain symptoms.

The studies were conducted with healthy women aged between 18–50 (a total of 858 randomised women) who had been using COCs in a 21/7 regimen for at least three cycles prior to the study and who had noted at least one symptom in the HFI of migraine or pelvic pain.

The primary objective was the change from baseline to cycle 6 in the average of the three highest visual analogue scale (VAS) scores for migraine and pelvic pain, assessed on days 22–28. The use of analgesics, symptoms linked to hormone use and quality of life were also considered in questionnaires and reliability was evaluated.

In both studies, E_2V/DNG triggered a marked reduction in the frequency and intensity of the symptoms of 'migraine and pelvic pain,' which was statistically significant versus the

comparator treatments. This improvement was also confirmed in the assessment of the secondary variables, making a 26/2 regimen a valid option for women who suffer from complaints related to the HFI.

The continuous use of COCs or a shorter pill break (for example, 24/4 vs 21/7) and maintenance of more stable oestrogens levels reduces the prevalence of the symptoms associated with hormonal suspension. Both the Harmony I[21] and Harmony II[22] studies indicate the superiority of the two-day HFI regimen versus the seven-day HFI regimen, thus supporting the working hypothesis that the shorter the HFI, the better it is in terms of menstrual migraine reduction.

[BOX]

Key points:

E_2V/DNG reduces the intensity of menstrual symptoms through two main mechanisms:

1. By offering constant levels of oestradiol around 50 picograms/mL (range 37–62), thus modulating and reducing the mast cell degranulation triggered by a more dramatic fall in the oestradiol and progesterone levels typical of the natural cycle (when oestradiol moves from 50–100 pg/mL after periods, up to 400–500 pg/mL at ovulation and around 200 pg/mL in the luteal phase).
2. By reducing the HFI to only two days, thus further reducing the mast cell degranulation and associated local and systemic inflammation.

[BOX ENDS]

Satisfaction and continuation rates

In clinical trials, E_2V/DNG was well tolerated and associated with a high degree of user satisfaction and a low discontinuation rate. Among nearly 1400 women who used E_2V/DNG for 20 cycles, 79.5% were satisfied or very satisfied with treatment. Treatment-related adverse events (considered at least possibly treatment-related) occurred in 19.8% of women and 10.2% of women prematurely discontinued treatment due to an adverse event.[60] This

rate compares favourably with discontinuation rates reported in the literature; it is estimated that around one-third of women starting OCs stop taking them within one year,[61] rising to more than 50% in adolescents.[62]

Sexual side effects of OCs

COCs can lead to sexual side effects, particularly a decrease in sexual desire and arousal.[63] Adverse effects on sexuality and mood are an important reason for discontinuation of COCs.[64] In a randomised, controlled study, half of women taking a COC reported reduced sexual interest.[65] It has been proposed that the adverse effects of COCs on sexual function are driven by iatrogenic testosterone deficiency; however, there is no specific level of testosterone below which female sexual dysfunction is more likely to occur.[66]

Progestins exhibit varying androgenic potency and it has been suggested that progestin formulations with stronger androgenicity, such as levonorgestrel (LNG), might be a better option for women with COC-associated side effects. However, this hypothesis is challenged by the STABLE study, an international double-blind clinical trial involving 213 women with COC-associated sexual dysfunction who were randomly assigned to E_2V/DNG, which contains a progestin with anti-androgenic activity, or to ethinylestradiol (EE) plus LNG, a strongly androgenic progestin.[67] After six treatment cycles, women in both treatment groups reported a highly significant improvement in sexual desire and arousal, with no between-group difference on any domain of the Female Sexual Function Index (Figure 8, 9).[68]

[Figure 8]

Female sexual dysfunction and vaginal health

Female sexual dysfunction is a multifactorial disorder and the impact of COCs on women's sexual function is likely to be complex (Figure 9). Beyond the androgenicity of the progestin component, COCs may have a negative impact on vaginal health. Exogenous oestrogen can increase levels of sex-hormone-binding globulin, leading to a reduction in testosterone

levels, which can contribute to vaginal atrophy.[68] COCs containing low doses of EE have been associated with decreased vaginal lubrication, up to severe vaginal dryness, which may contribute to dyspareunia and increased vulnerability to vulvar vestibulitis,[69] now known as "provoked vestibulodynia". Further important factors are the burden of menstrual-associated symptoms, length and regularity of menstrual bleeding and IDA, all of which may negatively influence sexual desire and mood.[70]

IDA is a common micronutrient deficiency and has been linked with anxiety and female sexual dysfunction (FSD). In a study involving more than 200 women of childbearing age with IDA, iron supplementation led to a significant reduction in anxiety and a significant improvement in female sexual function.[70] It is hypothesised that this association is mediated by the brain's dopaminergic system, which is particularly sensitive to dietary iron deficiency.[71]

[BOX]

Key point: The positive effect of E_2V/DNG on sexuality is likely to be rooted in different positive effects of this pill: maintaining iron levels with its positive effect on the dopaminergic system, which is involved in desire and sexual interest; reduced anaemia with higher physical and mental energy; a short HFI with reduced menstrual symptoms and effects on wellbeing; positive effect of oestradiol on vaginal lubrication (which is antagonised to a lesser extent by dienogest compared with other progestins); and, higher free testosterone, due to the reduced impact of estradiol, on sex-hormone-binding globulin in comparison to pills containing EE.

[BOX ENDS]

[Figure 9]

Summary and conclusions

Women today have many more periods in their lifetime than their ancestors. Menstrual bleeding is only necessary in women seeking to become pregnant and may be desired for cultural or personal reasons. However, it is not biologically necessary in women taking hormonal contraceptives. Furthermore, it may be advantageous for the women to have more stable levels of hormones throughout the cycle. The monthly fluctuations in oestrogens, progesterone and androgens are associated with a range of symptoms, both genital (i.e. vaginal bleeding, heavy menstrual bleeding, dysmenorrhoea and pelvic pain) and systemic (depression, fatigue, headache, IBS symptoms, asthma and allergy), triggered by a local and systemic rise in inflammatory molecules released by mast cells when oestrogens drop. These symptoms arise through a complex interaction between the endocrine and immune systems. Menstruation may thus be considered the genital sign of a local and systemic inflammatory event, characterised by an increase in mast cell degranulation and production of inflammatory molecules including cytokines.

COCs traditionally feature a seven-day HFI, during which menstruation occurs. Formulations with a shorter HFI (24/4 and 26/2) have recently been developed with the aim of offering a reduction in hormone withdrawal-associated symptoms together with more powerful ovarian suppression. E_2V/DNG is administered on a 26/2 regimen and has been shown to offer high contraceptive efficacy together with a reduction in heavy menstrual bleeding, improvement in hormone withdrawal-associated symptoms (including but not limited to headache and pelvic pain) and improvement in sexual function. E_2V/DNG may therefore be a good alternative to conventional 21/7 COCs for women with bothersome COC- or menstruation-related symptoms. Healthcare professionals should discuss these symptoms in women of reproductive age and raise awareness that treatment is available.

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Figure 1. Modern-day women experience three times as many periods as their predecessors.[25]

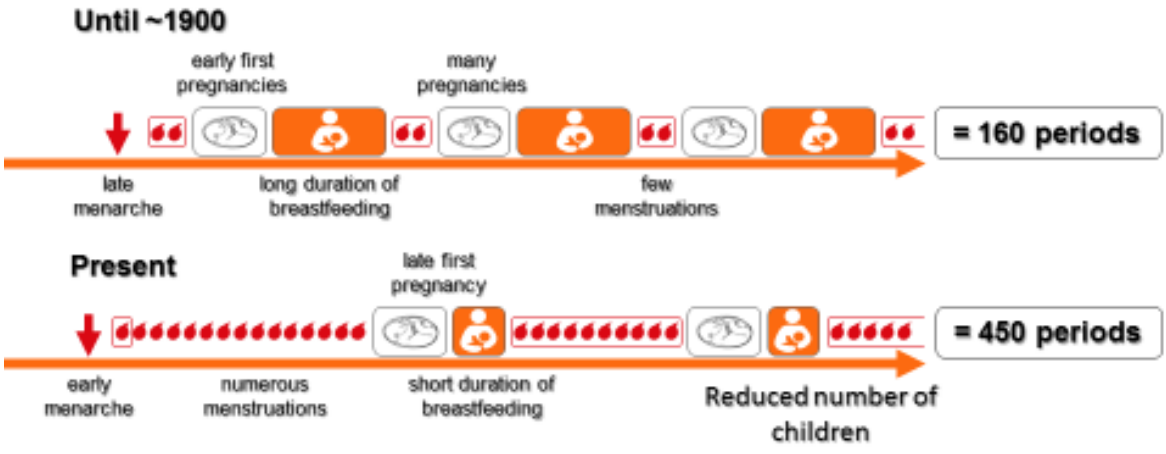


Figure 2. The perimenstrual phase, or luteo-follicular transition.[3, 27]

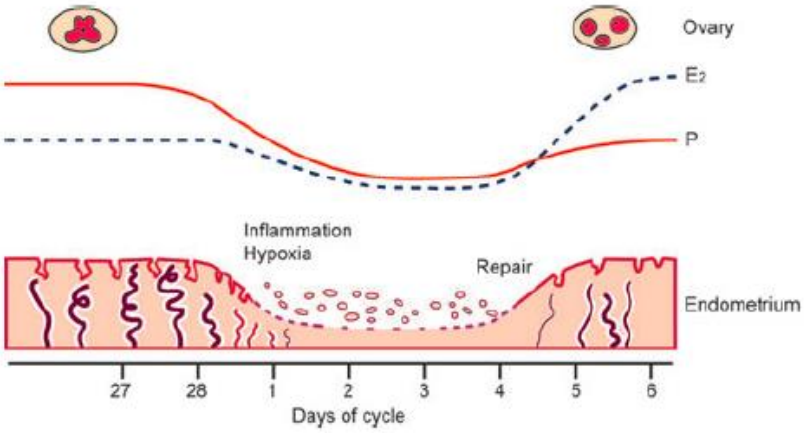
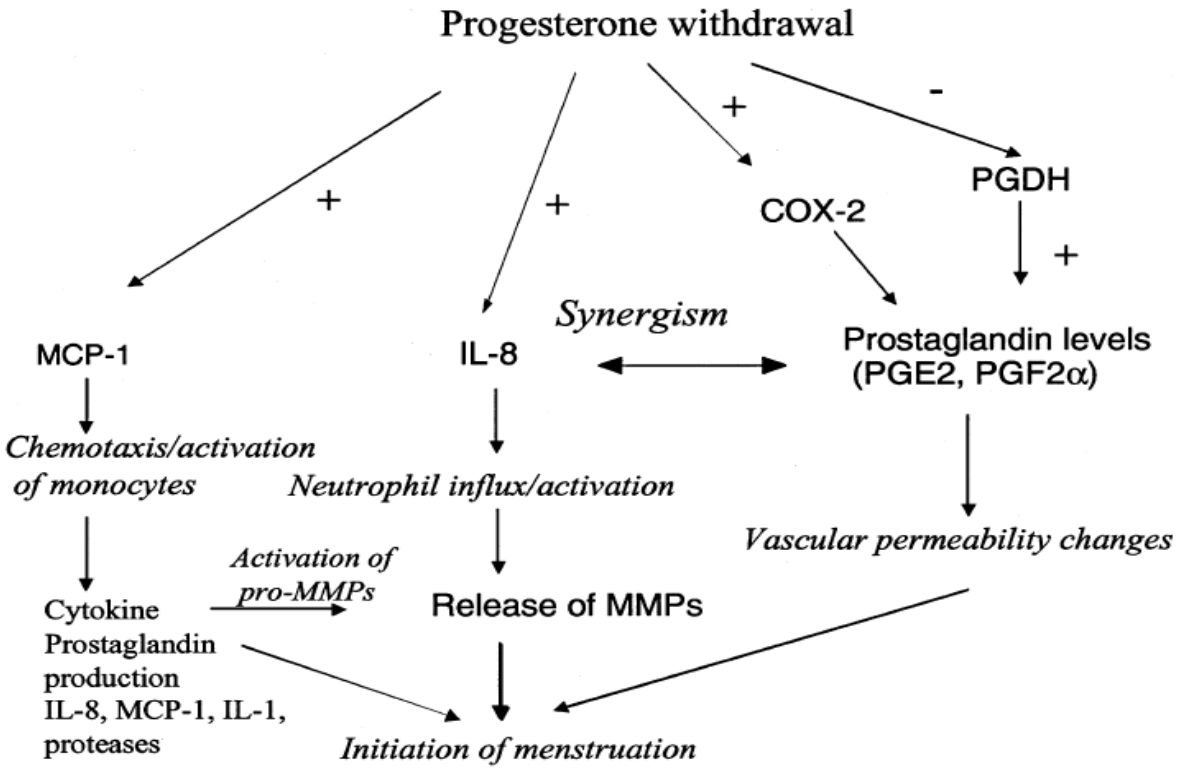


Figure 3. Menstrual hypothesis. Progesterone withdrawal has a pivotal role in initiating a cascade of hormonal and inflammatory events that culminate in menstrual bleeding.[1]



COX-2: cyclo-oxygenase-2; IL-1: interleukin-1; IL-8: interleukin-8; MCP-1: monocyte chemotactic protein 1; MMPs: matrix metalloproteinases; PGDH: 15-hydroxy prostaglandin dehydrogenase; PGE2: prostaglandin E2; PGF2α: prostaglandina F2α

Figure 4. Mean (± SD) symptom severity (A) and percentage of days with hard and soft stools (B) in women with irritable bowel syndrome (IBS) and control women without IBS. Symptom severity is measured daily on a 5-point scale 0 (none) to 4 (severe); values shown are averaged over a menstrual cycle. Repeated-measures analysis of variance was used to test group, menstrual cycle phase and interaction effects for each symptom or scale.[13]

* p<0.001 for between group comparison. p-value is significant after adjustment for 16 multiple comparisons in each column.

† p<0.05 for between phase comparison.

‡ p<0.05 for interaction.

§ p<0.001 for between phase comparison. p-value is significant after adjustment for 16 multiple comparisons in each column.

# p<0.001 for interaction. p-value is significant after adjustment for 16 multiple comparisons in each column.

¶ p<0.05 for between phase comparison. p-value is significant after adjustment for 16 multiple comparisons in each column.

€ p<0.05 for interaction. p-value is significant after adjustment for 16 multiple comparisons in each column.

α p<0.05 for between group comparison.

β p<0.001 for between group comparison

[Reproduced from Heitkemper et al. 2003[13]]

Table 1. Mean (± SD) Symptom Severity in Women With IBS and Control Women Without IBS*

	IBS (n = 149)	Control (n = 42)	Significance†		
			Group	Phase	Interaction
Symptom subscales					
GI	0.91 ± 0.53	0.18 ± 0.20	<0.001‡	0.021	
Somatic	0.73 ± 0.56	0.29 ± 0.22	<0.001‡	<0.001‡	
Menstrual	0.72 ± 0.46	0.27 ± 0.26	<0.001‡	<0.001‡	
Sleep	0.72 ± 0.66	0.37 ± 0.42	0.001‡		
Cognitive	0.54 ± 0.59	0.22 ± 0.32	0.001‡		
Anxiety	0.71 ± 0.56	0.39 ± 0.46	0.001‡	0.020	
Depressive	0.59 ± 0.55	0.25 ± 0.27	<0.001‡	0.021	
Anger	0.78 ± 0.52	0.44 ± 0.37	<0.001‡	0.003‡	
Individual symptoms					
Abdominal pain	1.14 ± 0.74	0.19 ± 0.33	<0.001‡	0.102	
Intestinal gas	1.60 ± 0.93	0.29 ± 0.44	<0.001‡		
Bloating	1.15 ± 0.88	0.33 ± 0.41	<0.001‡	<0.001‡	
Constipation	0.87 ± 0.87	0.11 ± 0.19	<0.001‡	0.153	
Diarrhea	0.44 ± 0.46	0.12 ± 0.18	<0.001‡		
Uterine cramps	0.65 ± 0.55	0.29 ± 0.29	<0.001‡	<0.001‡	
Percentage of days with:					
Hard stools	24 ± 23	14 ± 21	0.017‡		
Loose stools	31 ± 25	9 ± 13	<0.001‡		0.150

* Symptom severity is measured daily on a 5-point scale of 0 (none) to 4 (severe); values shown are averaged over a menstrual cycle.
† Repeated-measures analysis of variance was used to test group, menstrual cycle phase, and interaction effects for each symptom or scale. If no value is shown, *p* value is >0.20.
‡ *P* value is significant after adjustment for the 16 multiple comparisons in each column.

Figure 5. Levels of oestradiol and inhibin-B with a seven-day versus three-day or four-day hormone-free interval. [Reproduced from Willis et al. 2006 [15]]

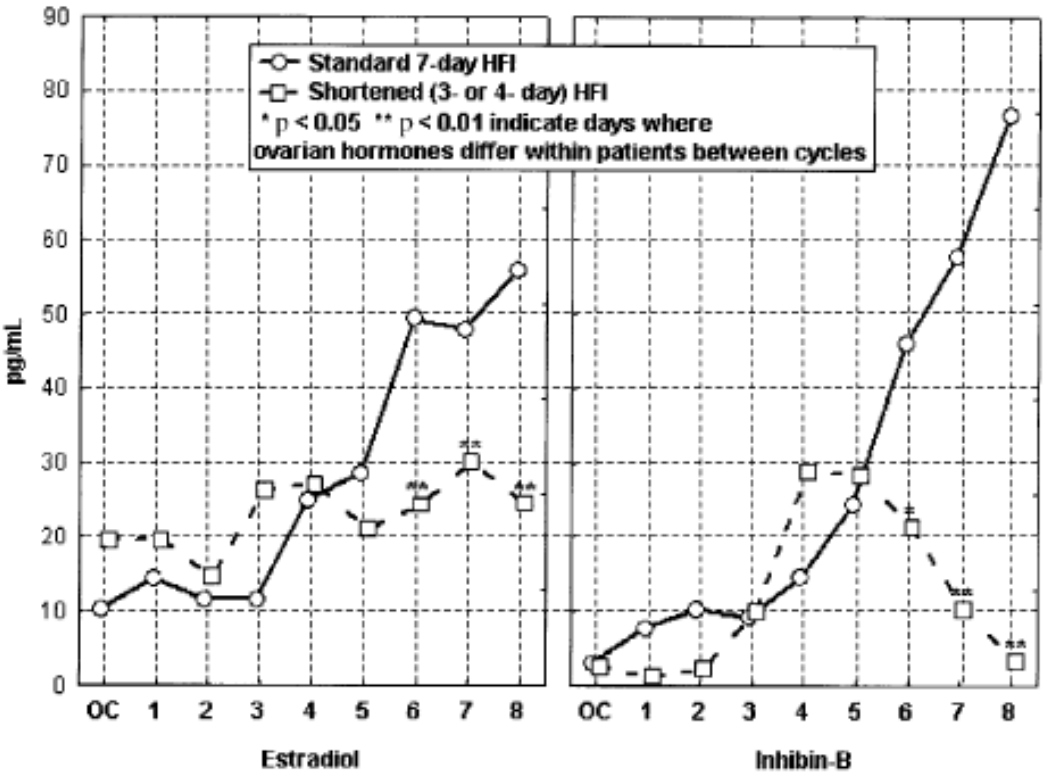


Figure 6. Menstruation-associated symptoms and analgesic use are significantly more prevalent during the hormone-free interval than during active treatment with combined oral contraceptives.[14]

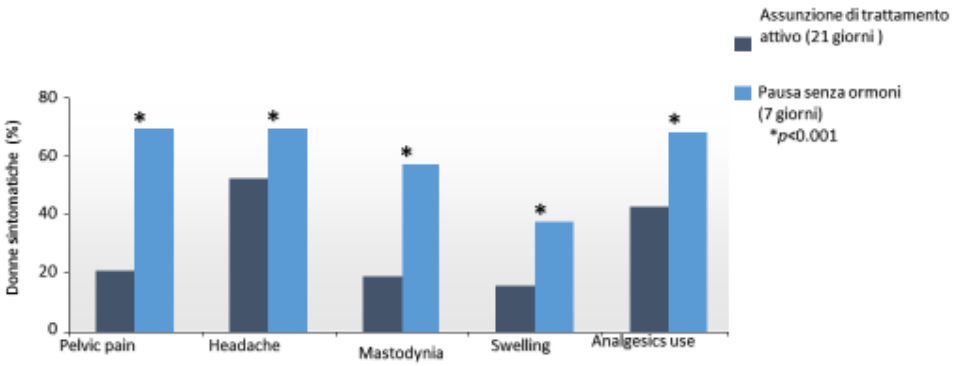


Figure 7. Median menstrual blood loss by treatment cycle in women treated with oestradiol valerate/dienogest (E_2V/DNG) versus placebo. [Reproduced from Fraser et al. 2011 [56]]

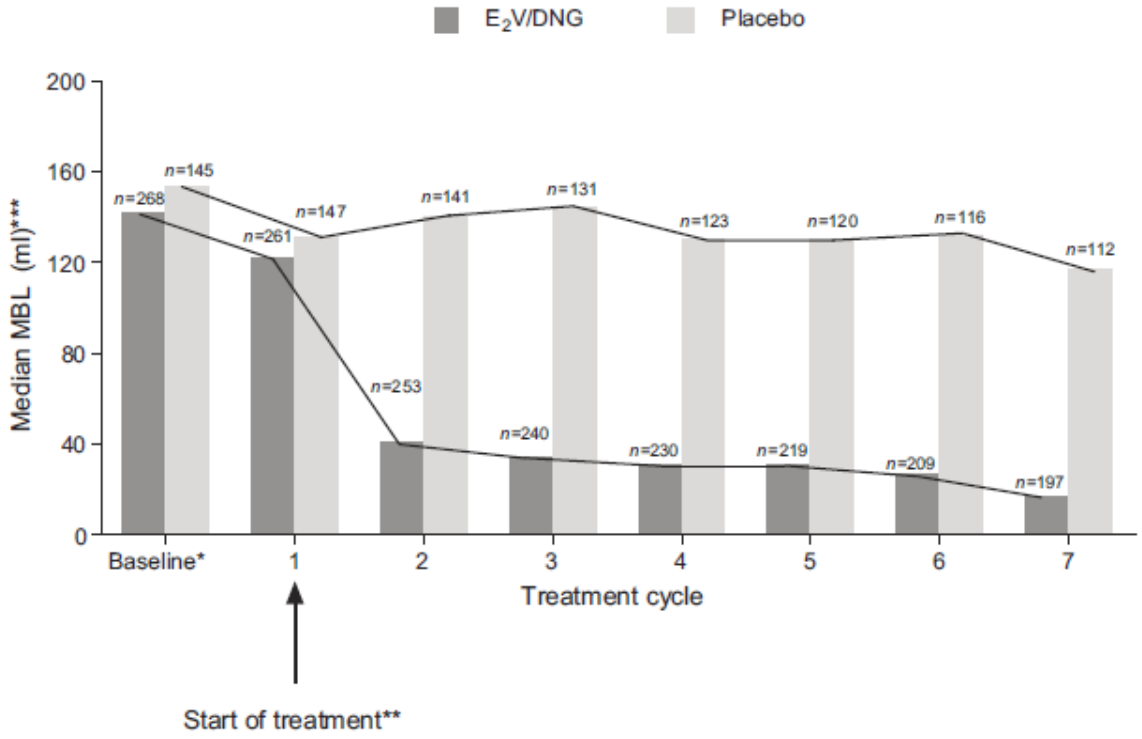


Figure 8. Similar improvement in sexual desire and arousal with an androgenic COC (EE/LNG) or an anti-androgenic COC (E_2V/DNG) in women with COC-associated sexual dysfunction between baseline and cycle 6.[66] Scores for combined domains range from 2 to 30. An increase in score represents an improvement in symptoms.

FSD: female sexual dysfunction

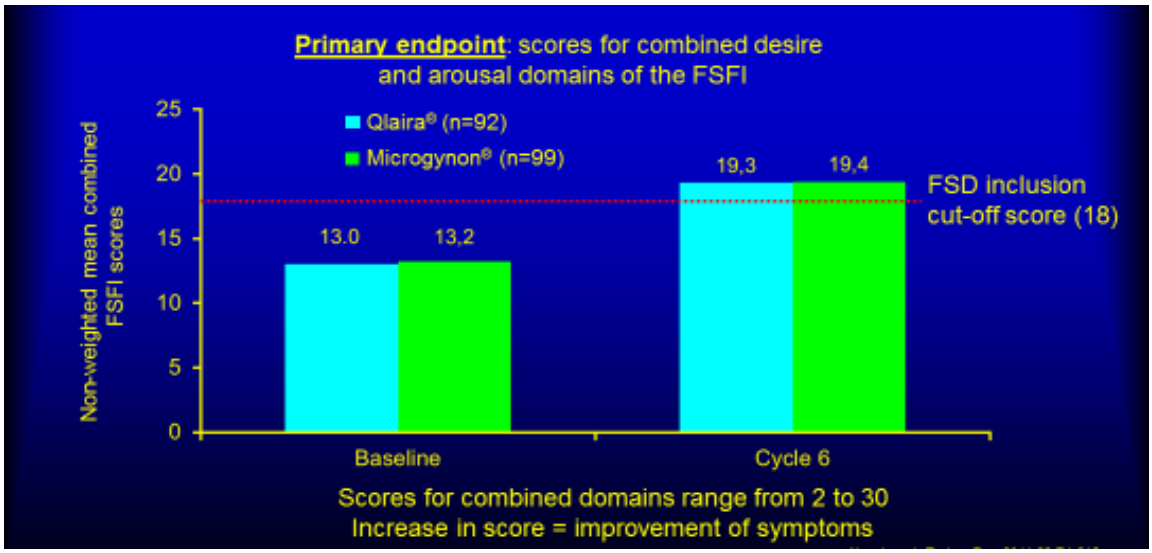


Figure 9. Factors contributing to the positive effect of E_2V/DNG pill on women's sexuality.[8]