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Low-Dose Ethinylestradiol/ Levonorgestrel

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Contents

Abstract

▲ Low-dose ethinylestradiol/levonorgestrel 20μg/100μg is a combined oral contraceptive that prevents pregnancy primarily by inhibiting ovulation.

▲ The Pearl index (pregnancies per 100 woman-years of use) with ethinylestradiol/levonorgestrel 20μg/100μg was 0.88 and the cumulative pregnancy rate was 1.9% at the end of a 3-year open-label trial (1708 women with 26 554 evaluable cycles). The contraceptive efficacy of ethinylestradiol/levonorgestrel 20μg/100μg was similar to that of other low-dose combined oral contraceptives containing ethinylestradiol 20 or 35μg in a 6-cycle trial (463 evaluable women).

▲ Ethinylestradiol/levonorgestrel 20μg/100μg is well tolerated; adverse events were those commonly associated with combined oral contraceptives. Headache and metrorrhagia (2% of women) were the most common adverse events leading to treatment discontinuation in the 3-year trial.

▲ Cycle control in open-label trials in women receiving up to 36 cycles of ethinylestradiol/levonorgestrel 20μg/100μg was generally good, with the incidence of intermenstrual bleeding being highest during the first few cycles of use and decreasing thereafter.

Features and properties of low-dose ethinylestradiol/levonorgestrel 20μg/100μg (Alesse®, Leios®, Loette®)		
Indication		
Prevention of pregnancy		
Mechanism of action		
Suppresses ovulation, thickens cervical mucus, suppresses proliferation of the endometrium		
Dosage and administration		
Recommended dosage	20μg/100μg	
Route of administration	Oral	
Frequency of administration	Once daily for 21 days of a 28-day cycle	
Pharmacokinetic profile following once-daily oral administration for 21 days to 22 healthy women (mean values)		
	Ethinylestradiol	*Levonorgestrel*
Area under the serum concentration-time curve	776 pg • h/mL	68.3 ng • h/mL
Maximum serum concentration (C_{max})	82.3 pg/mL	6.0 ng/mL
Time to C_{max}	1.4h	1.5h
Most common adverse events (>2% of patients)		
Headache, metrorrhagia, dysmenorrhoea and nausea		

The oral contraceptive pill was the most commonly used method of birth control in recent studies in Europe[1] and the US.[2] Oral contraceptives were currently being used by 19% of the 7643 women (aged 15–44 years) surveyed in 2002 in a US study[2] and by 30% of the 12 138 women (aged 15–49) surveyed in 2003 in a European study.[1]

Combined oral contraceptives (COCs) contain synthetic estrogens and progestogens, and prevent pregnancy primarily by inhibiting ovulation.[3] Since their introduction in the 1960s, the doses used in COCs have been steadily reduced in order to improve tolerability.[4] It has been demonstrated that levonorgestrel combined with ethinylestradiol in a 5 : 1 ratio provides good contraceptive efficacy with an acceptable safety profile.

This review provides an overview of the contraceptive efficacy and tolerability of low-dose oral ethinylestradiol/levonorgestrel 20μg/100μg administered once daily for 21 days of a 28-day cycle; discussion is limited to the drug marketed under the trade names Alesse®, Leios® and Loette®.[1]

1. Pharmacodynamic Profile

COCs act primarily by inhibiting ovulation (by the suppression of gonadotropin release);[3] they also cause a thickening of cervical mucus (making sperm entry into the uterus more difficult) and suppress proliferation of the endometrium (reducing the likelihood of implantation).[5] This section focuses on published data pertaining specifically to ethinylestradiol/levonorgestrel 20μg/100μg administered once daily for 21 days of a 28-day cycle.

Effects on Ovarian Activity

- Ovarian activity, as assessed by mean follicular size and mean serum progesterone levels, was suppressed by ethinylestradiol/levonorgestrel 20μg/100μg in two 3-cycle trials in evaluable healthy women aged 18–35 years (n = 13[6] and 24[7]). In both trials,[6,7] ovulation was confirmed during a pretreatment cycle. Although some follicular activity occurred during use of ethinylestradiol/levonorgestrel 20μg/100μg, ovulation was suppressed in all 43 cycles in one study[6] and in 71 of 73 cycles (97%) in the other study.[7]
- Ovarian activity was restored after treatment was discontinued, as reflected by mean serum progesterone levels.[7]

Effects on Serum Lipid Levels

- Ethinylestradiol/levonorgestrel 20μg/100μg was not associated with any significant mean percentage changes from baseline in the serum levels of total or high-density lipoprotein (HDL)-cholesterol during any of the cycles of a 24-month study in 28 evaluable healthy women aged 19–44 years.[8] In addition, HDL subfraction 2, apolipoprotein A-1 or the ratios of HDL subfractions 2 to HDL subfractions 3 were not significantly changed from baseline.
- Significant changes from baseline occurred in other lipid parameters during treatment in this trial; however, these changes were similar to those seen with other low-dose oral contraceptives and were no longer significant by cycle 24.[8] During cycles 3–18, increases occurred in the levels of low-density lipoprotein (LDL)-cholesterol (9–11%; $p \leq 0.05$), triglycerides (31–40%; $p \leq 0.01$) and apolipoprotein B (22–25%; $p \leq 0.001$), the ratio of apolipoproteins B to A-1 (23–33%; $p \leq 0.001$) and in the ratios of LDL- to HDL-cholesterol (11–13%; $p \leq 0.05$) and total cholesterol to HDL-cholesterol (8%; $p \leq 0.05$).[8]
- Mean changes in triglyceride levels from baseline (26% vs 21%) were not significantly different in recipients of ethinylestradiol/levonorgestrel 20μg/100μg compared with those in recipients of triphasic ethinylestradiol/norethindrone (administered at a dosage of 35μg/500μg, 35μg/750μg and 35μg/1000μg for 7 days each) in a 4-cycle multicentre trial in 235 evaluable women.[9] However, the mean increase in total cholesterol was significantly lower with ethinylestradiol/levonorgestrel than with triphasic ethinylestradiol/norethindrone (4.9% vs 10.9%; $p < 0.05$).

1 The use of trade names is for identification purposes only and does not imply endorsement.

Effects on Haemostatic Factors

• Ethinylestradiol/levonorgestrel 20μg/100μg increased procoagulant and fibrinolytic activity, but haemostatic determinants generally remained within the reference ranges and the changes were not considered to be clinically important, according to a 12-cycle open-label study in 30 healthy women (mean age 30 years).[10] Factor X, plasminogen antigen and activity and D-dimer levels increased significantly from baseline during cycles 3, 6 and 12 ($p \leq 0.01$). Significant decreases from baseline occurred in antithrombin antigen and protein S total antigen during these three cycles ($p \leq 0.001$), in protein S activity levels at cycle 3 and 6 ($p < 0.05$) and in factor VII levels at cycle 3 ($p < 0.05$).

2. Pharmacokinetic Profile

The data regarding the pharmacokinetics of ethinylestradiol/levonorgestrel 20μg/100ug reported in this section were obtained from the US manufacturer's prescribing information.[5]

• The bioavailability of ethinylestradiol/levonorgestrel 20μg/100μg has not been specifically investigated.[5] However, orally administered levonorgestrel is rapidly and completely absorbed, is not subject to appreciable first-pass metabolism and is approximately 100% bioavailable. Ethinylestradiol is also rapidly and almost completely absorbed following oral administration. It undergoes first-pass metabolism in the gut and liver, and its bioavailability is ≈38–48%.

• In 22 women receiving oral ethinylestradiol/levonorgestrel 20μg/100μg once daily for 21 days,[5], the mean area under the serum concentration-time curve (AUC), the mean maximum serum concentration (C_{max}) and mean time to reach C_{max} were 776 pg • h/mL, 82.3 pg/mL and 1.4 hours; respective values for levonorgestrel were 68.3 ng • h/mL, 6.0 ng/mL and 1.5 hours.

• Ethinylestradiol is highly bound (≈97%) to plasma albumin.[5] In serum, levonorgestrel binds mainly to sex hormone binding globulin (SHBG); ethinylestradiol induces SHBG synthesis, but does not bind to SHBG. Because of these properties, the kinetics of levonorgestrel are non-linear; over time there is an increase in binding of the drug to SHBG, as the levels of SHBG are increased by the daily administration of ethinylestradiol.

• Ethinylestradiol is metabolised primarily by hydroxylation by cytochrome P450 (CYP) enzymes.[5] The 2-hydroxy metabolite further is transformed by methylation and glucuronidation. Ethinylestradiol undergoes enterohepatic circulation and is excreted in the urine and faeces as glucuronide and sulphate conjugates.[5] Levonorgestrel is extensively metabolised by the liver to a large number of inactive metabolites; the primary metabolites circulating in the blood are sulphates of 3α,5β-tetrahydro-levonorgestrel.[5] Additionally, some of the parent levonorgestrel circulates as a 17β-sulfate conjugate. Levonorgestrel and its metabolites (primarily glucuronide conjugates) are excreted in the urine (40–68%) and faeces (≈16–48%).

• At steady state, the elimination half-lives of levonorgestrel and ethinylestradiol were ≈36 and 18 hours.[5]

• Race does not appear to affect the pharmacokinetic parameters of ethinylestradiol and levonorgestrel following the oral administration of ethinylestradiol/levonorgestrel 20μg/100μg.[5] No pharmacokinetic studies of ethinylestradiol/levonorgestrel 20μg/100μg have been performed in women with renal or hepatic disease. In women with impaired liver function, steroid hormones may be poorly metabolised.

Drug Interactions

• The contraceptive effectiveness of oral contraceptives may be reduced by coadministration with antibiotics, anticonvulsants, anti-HIV protease inhibitors and herbal products containing St John's wort.[5]

• Coadministration of atorvastatin may increase the AUC of ethinylestradiol by ≈20%, while ascorbic acid and paracetamol (acetaminophen) may increase the bioavailability of ethinylestradiol.[5] Agents that inhibit CYP3A4, such as indinavir, fluconazole, itraconazole and troleandomycin, may increase plasma levels of hormones; coadministra-

tion of troleandomycin with oral contraceptives may also increase the risk of intrahepatic cholestasis.

- Coadministration of oral contraceptives may increase plasma concentrations of cyclosporin, corticosteroids (e.g. prednisolone) and theophylline, decrease plasma concentrations of paracetamol (acetaminophen) and increase clearance of temazepam, salicylic acid, morphine and clofibric acid.[5]

3. Therapeutic Use

Contraception

The efficacy of ethinylestradiol/levonorgestrel 20μg/100μg as an oral contraceptive has been assessed in two open-label, multicentre trials in women who had normal menstrual cycles and were at risk of becoming pregnant.[4,11] In both studies, ethinylestradiol/levonorgestrel 20μg/100μg was administered once daily on days 1–21 of the 28-day cycle and followed by 7 days of placebo.

In one 3-year study,[4] women (n = 1708) were aged 17–49 (mean 27) years; the trial was closed after 20 000 cycles. In the other study,[11] 463 women aged 18–49 years were randomised to receive one of three regimens for 6 cycles: an ethinylestradiol/levonorgestrel 20μg/100μg regimen; an ethinylestradiol/desogestrel regimen (ethinylestradiol/desogestrel 20μg/150μg for days 1–21, then 2 hormone-free days, then ethinylestradiol 10μg for 5 days); or an ethinylestradiol/norgestimate regimen (ethinylestradiol/norgestimate 35μg/180μg on days 1–7, 35μg/215μg on days 8–14 and 35μg/250μg on days 15–21, then 7 hormone-free days).

The majority of women had used another oral contraceptive within 3 months of starting study drug (61%[4] and 62–71%[11]), whereas 5.1%[4] and 6–11%[11] had never used an oral contraceptive.

Efficacy was assessed according to the incidence of pregnancies during the study.[4,11] Both trials used the Pearl index (the number of pregnancies per 100 women-years of oral contraceptive use over all cycles) and life-table analyses, which provided estimates of the likelihood of a pregnancy within a specific period of oral contraceptive use. In the larger trial,[4] a cycle was excluded from analysis if a woman missed more than three consecutive active tablets in that cycle, and the woman was then withdrawn from the study.

- Ethinylestradiol/levonorgestrel 20μg/100μg was an effective contraceptive, with Pearl indices of 0.88[4] and 1.5[11] at study end in the two open-label trials. In the larger trial (26 554 evaluable cycles),[4] 18 women became pregnant over the 3-year study; six of these pregnancies were attributable to non-compliance of the women (i.e. missing more than one active tablet in the cycle in which conception occurred or in the cycle just prior to conception). In a separate analysis of the 218 women aged ≥35 years enrolled in this study (3859 evaluable cycles),[12] one woman became pregnant, yielding a Pearl index of 0.34. In the smaller study,[11] one woman receiving ethinylestradiol/levonorgestrel group became pregnant over the 6-month study.
- The cumulative withdrawal rates of women from the larger study because of accidental pregnancy were 0% after 3 cycles and 1.9% after 30 cycles.[4]
- The contraceptive efficacy of ethinylestradiol/levonorgestrel 20μg/100μg was similar to that of other low-dose oral contraceptives containing ethinylestradiol 20 or 35μg.[11] In the 6-cycle study, there were no significant between-group differences in the Pearl indices of the three treatment regimens.[11] One woman in the ethinylestradiol/levonorgestrel group, three in the ethinylestradiol/norgestimate group and none in the ethinylestradiol/desogestrel group became pregnant, giving Pearl indices of 1.5, 4.4 and 0. Respective cumulative pregnancy rates over the 6 cycles were 0.007, 0.021 and 0 (based on life-table analyses).

Dysmenorrhoea

The efficacy of ethinylestradiol/levonorgestrel 20μg/100μg as treatment for moderate or severe dysmenorrhoea in adolescents was assessed in a 3-month, randomised, double-blind, placebo-controlled trial in 76 adolescents aged ≤19 (mean 17) years.[13] The adolescents had normal menstrual cycles for at least 1 year and did not require the use of a

contraceptive; the usual pain medication was continued as required. Ethinylestradiol/levonorgestrel 20μg/100μg was administered once daily on days 1–21 of the 28-day cycle and followed by 7 days of placebo. The primary endpoint was the score on the Moos Menstrual Distress Questionnaire (MMDQ) pain subscale (mean 12.6 for the worst score) after three cycles of treatment. The intensity of the worst pain was also rated (0–10 scale)

- Dysmenorrhoea-associated pain was significantly less in recipients of ethinylestradiol/levonorgestrel than placebo after 3 months of treatment (MMDQ score 3.1 vs 5.8; p = 0.004).[13]
- Recipients of ethinylestradiol/levonorgestrel, compared with recipients of placebo, rated their worst pain as less (score 3.7 vs 5.4; p = 0.02) and required significantly fewer pain medications (1.3 vs 3.7 pain pills; p = 0.05).[13]

4. Tolerability

Overall Profile

The overall tolerability profile of ethinylestradiol/levonorgestrel 20μg/100μg was investigated in the 6-cycle[11] and 3-year[4] trials summarised in section 3. Tolerability data are also available from a combined analysis of two phase III, randomised, double-blind, placebo-controlled, multicentre, 6-cycle trials (n = 704) of the contraceptive in the treatment of acne.[14] In all trials, ethinylestradiol/levonorgestrel 20μg/100μg was administered once daily on days 1–21 of the 28-day cycle and followed by 7 days of placebo.

- Ethinylestradiol/levonorgestrel 20μg/100μg is well tolerated. The adverse events reported in the clinical trials[4,11,14] were those commonly associated with COCs.
- In the combined analysis of the two placebo-controlled 6-cycle trials,[14] the percentage of women who reported one or more adverse event was not significantly different between those receiving ethinylestradiol/levonorgestrel 20μg/100μg or placebo (82.0% vs 76.9%). There was no significant between-group difference in the incidence of estrogen-related adverse events, including headache, nausea, breast pain, weight gain (figure 1), migraine and vomiting. However, metrorrhagia, menstrual disorder, allergic reaction, menorrhagia and urticaria occurred in significantly more recipients of ethinylestradiol/levonorgestrel than placebo ($p < 0.05$); only one of the allergic reactions was considered by the investigator to be treatment related.
- In an interim analysis (1477 women with 7870 cycles of exposure)[15] of the 3-year trial (section 3), 38% of women reported an adverse event that was considered to be at least possibly related to treatment with ethinylestradiol/levonorgestrel. The most common adverse events were headache (14% of women), metrorrhagia (8%), dysmenorrhoea (7%) and nausea (7%). Other adverse events included abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhoea (2%) and vaginal moniliasis (2%).
- In the final analysis of the 3-year trial (1708 women), 17% of women discontinued treatment with ethinylestradiol/levonorgestrel because of one or more adverse events.[4] The most common events that caused women to discontinue treatment were

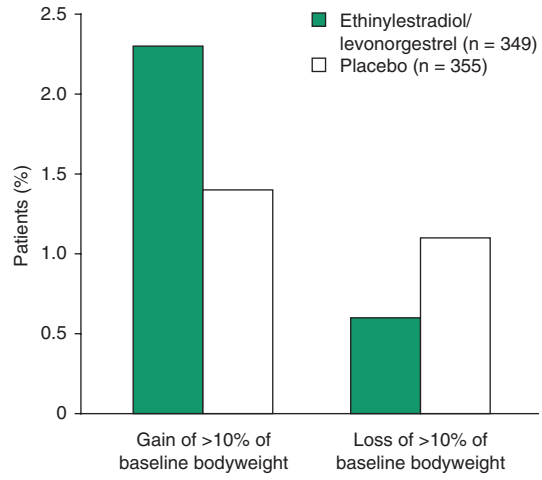

Fig. 1. Percentage of women gaining or losing >10% of baseline bodyweight with ethinylestradiol/levonorgestrel. Combined analysis of two phase III, randomised, double-blind, placebo-controlled, multicentre, 6-cycle trials (n = 704) in women with acne.[14] Ethinylestradiol/levonorgestrel 20μg/100μg was administered once daily on days 1–21 of the cycle and followed by 7 days of placebo.

metrorrhagia and headache (both 2% of women). Other events leading to withdrawal (<1% of women) were hypertension, migraine, nausea, hypercholesterolaemia, weight gain, depression, emotional lability, decreased libido, acne, amenorrhoea and menorrhagia.

- The US manufacturer's prescribing information indicates that oral contraceptives may increase the risks of myocardial infarction, venous thromboembolism (VTE) and cerebrovascular disease.[5] No such events were reported in the 3-year[4] or 6-cycle[11,14] trials, except one incidence of myocardial infarction (resulting in withdrawal from the trial) reported in the 3-year trial[4] in a woman who smoked heavily.

- The European Medicines Agency (EMEA) public assessment report on COCs and VTE notes that the magnitude of the absolute increased risk of VTE associated with COCs containing <50μg of ethinylestradiol and a progestogen is small (≈20 cases per 100 000 women-years of use), with the overall balance of benefits and risks being in favour of the COC.[16] The EMEA also note that the increased risk of VTE associated with use of COCs is less than that associated with pregnancy.[16]

- Women using third-generation COCs (ethinylestradiol ≥20μg with desogestrel or gestodene as a mono-, bi-, or triphasic formulation) have an increased risk of VTE compared with women using second-generation COCs (ethinylestradiol <50μg with a progestogen [commonly levonorgestrel]), with a relative risk of 1.5–2.0.[16] Compared with the use of a second-generation COC, an additional 10–20 cases of VTE per 100 000 women-years of use would occur with the use of a third-generation COC.

- The excess risk of VTE is greatest during the initial year that a women uses a COC.[16] Taking into account the relative risk of VTE with third-generation COCs, compared with second-generation COCs, the number of new cases of VTE in users of third-generation COCs is likely to be greatest during this time period. The EMEA report recommends that this information should be taken into account when any COC is used for the first time by a woman.[16]

- Mean changes in bodyweight were similar in ethinylestradiol/levonorgestrel and placebo recipients in the combined analysis of the two placebo-controlled 6-cycle trials.[14] At study end, the respective changes in mean bodyweight from baseline were 0.72 and 0.56kg. A similar percentage of patients gained or lost <1 or ≥1kg at study end, with a low percentage of patients losing or gaining >10% of their baseline bodyweight (figure 1).

- Blood pressure (BP) generally remained unchanged in recipients of ethinylestradiol/levonorgestrel 20μg/100μg.[4,14] In the combined analysis of the two phase III 6-cycle trials,[14] there was no significant between-group difference in recipients of ethinylestradiol/levonorgestrel or placebo for mean systolic or diastolic sitting BP at any time point, except for a higher mean change from baseline in systolic BP with ethinylestradiol/levonorgestrel compared with placebo during cycle 1 (+1.05 vs −1.01mm Hg; p = 0.038).[14] In the 3-year trial,[4] 4% of ethinylestradiol/levonorgestrel recipients had an elevated systolic (≥140mm Hg) or diastolic (≥90mm Hg) BP at least once during the study. However, 81% of these women either remained in the study, with no further episodes of elevated clinical hypertension or withdrew from the study for other reasons.

Menstrual Cycle Control

Intermenstrual bleeding has been reported in women taking low-dose oral contraceptives,[3] with a variation in intensity characterised by spotting (light flow that did not necessitate sanitary protection) or bleeding that was normal to heavy and required sanitary protection.

Cycle control with ethinylestradiol/levonorgestrel 20μg/100μg was investigated in the 6-cycle[11] and 3-year[4] open-label trials discussed in section 3. Cycle control in recipients of ethinylestradiol/levonorgestrel 20μg/100μg has also been compared with that of ethinylestradiol/norethindrone (monophasic[17] or triphasic[9,18]) regimens in three 4-cycle randomised, open-label, multicentre trials.[9,17,18]

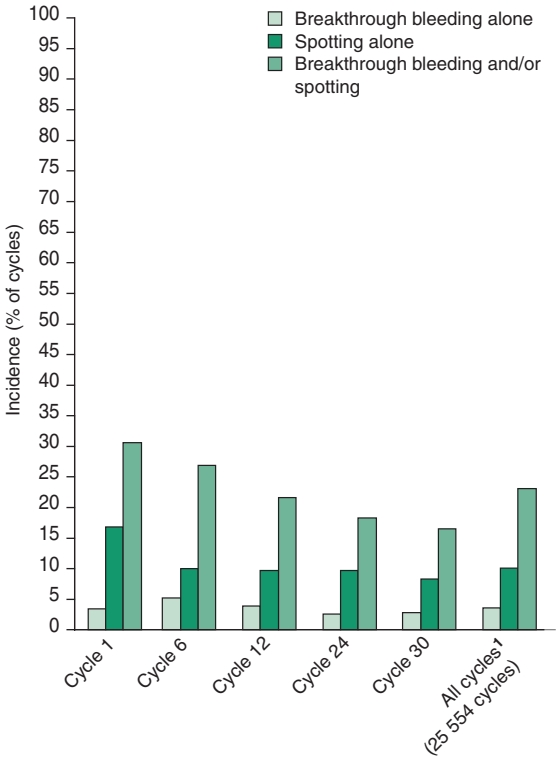

Fig. 2. Cycle control in women receiving ethinylestradiol/levonorgestrel 20μg/100μg.[4] Healthy women (n = 1708) with normal menstrual cycles received one active tablet per day for 21 days, then placebo for 7 days each cycle, for up to 3 years. Spotting was defined as light flow that did not necessitate sanitary protection. Bleeding was defined as a heavier flow that necessitated sanitary protection. Breakthrough bleeding or spotting was defined as bleeding or spotting that occurred on days 5–21, or on days 1–4 if preceded by 2 consecutive days without spotting. **1** Excluding cycle 1.

In all trials, ethinylestradiol/levonorgestrel 20μg/100μg was administered for days 1–21 of the 28-day cycle and followed by 7 days of placebo. In the comparative trials, monophasic ethinylestradiol/norethindrone was administered at a dosage of 20μg/1000μg for 21 days per cycle in one trial (n = 120 evaluable women)[17] and triphasic ethinylestradiol/norethindrone was administered at a dosage of 35μg/500μg, 35μg/750μg and 35μg/1000μg for 7 days each in the other two trials (n = 220 evaluable women[9] and 191[18]).

- Cycle control in open-label trials in women receiving up to 36 cycles of ethinylestradiol/levonorgestrel 20μg/100μg was generally good, with the incidence of intermenstrual bleeding being highest during the first few cycles of use and decreasing thereafter.[4,9,11,17,18] In the 3-year trial,[4] the incidence of breakthrough bleeding, spotting or both was 31% during cycle 1, but had decreased to 16.5% by cycle 30; the overall incidence (excluding cycle 1) was 23.1%. The incidence of spotting alone was generally low and <10% after cycle 6 (figure 2). Amenorrhoea occurred in 1.9% of cycles.[4]
- The mean duration of withdrawal bleeding was 4.7 (range 1–11) days in ethinylestradiol/levonorgestrel recipients in the 3-year trial.[4] Withdrawal bleeding lasted for 3–7 days in 92% of cycles. Excluding cycle 1, the mean cycle length was 29.1 days, with the cycle length ranging from 26 to 30 days for 92.2% of the cycles.
- In two comparative 4-cycle trials, the incidence of breakthrough bleeding and/or spotting was similar in recipients of ethinylestradiol/levonorgestrel or triphasic ethinylestradiol/norethindrone.[9,18] However, the incidence of intermenstrual bleeding was lower in ethinylestradiol/levonorgestrel recipients than in recipients of monophasic ethinylestradiol/norethindrone in a third study (36% vs 53%), with the between-group difference being significant during cycles 2 and 3 ($p < 0.05$).[17]
- Amenorrhoea occurred with a similar incidence in ethinylestradiol/levonorgestrel and triphasic ethinylestradiol/norethindrone recipients (4% vs 3%) in two of the studies.[9,18] However, the overall incidence of amenorrhoea was lower in recipients of ethinylestradiol/levonorgestrel than monophasic ethinylestradiol/norethindrone in the third study (1% vs 10%), with the between-group difference being significant during cycles 1 and 2 ($p < 0.05$).[17]

5. Dosage and Administration

For the prevention of pregnancy, ethinylestradiol/levonorgestrel 20μg/100μg should be taken once daily for 21 days, followed by once-daily placebo tablets for 7 days, every cycle.[5] It is recommended that ethinylestradiol/levonorgestrel 20μg/100μg should be taken at the same time each day and at intervals not exceeding 24 hours. Practitioners pre-

scribing oral contraceptives should be aware of the increased risk of several serious conditions, including myocardial infarction, thromboembolism and cerebrovascular disease. Local prescribing information should be consulted for contraindications, warnings and precautions.

6. Low-Dose Ethinylestradiol/ Levonorgestrel: Current Status

In the US, several European and other countries, ethinylestradiol/levonorgestrel 20μg/100μg is approved for the prevention of pregnancy.[5] The drug was effective in this indication in two large trials (treatment duration up to 3 years) and is generally well tolerated. Data from a 3-month randomised, double-blind trial also indicated that ethinylestradiol/levonorgestrel 20μg/100μg was effective in reducing dysmenorrhoea-associated pain in adolescents.

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