CHAPTER 2

Quadriphasic versus monophasic oral contraceptives for contraception

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Abstract

Background

Quadriphasic oral contraceptives have been developed to reduce the adverse effects of oral contraceptives and are presented as more physiological since theymimic the natural cycle. However, suggested disadvantages of quadriphasic oral contraceptives include a possible increased risk of pill-taking errors caused by the array of different color pills, complicated directions for catching up when a pill is missed, the higher price and potential inferiority in terms of side effects.

Objectives

To compare the contraceptive effectiveness, bleeding pattern, minor side effects and acceptability of quadriphasic contraceptive pills versus monophasic contraceptive pills.

Search methods

We searched CENTRAL, MEDLINE, EMBASE, POPLINE, ClinicalTrials.gov and ICTRP for trials comparing quadriphasic pills with monophasic pills. We contacted researchers and manufacturers of quadriphasic oral contraceptives to identify additional studies.

Selection criteria

Randomized controlled trials (RCTs) comparing quadriphasic with monophasic oral contraceptives. Trials had to report on contraceptive effectiveness, bleeding patterns, minor side effects, ease of use or trial discontinuation. We excluded studies where the intervention was primarily used as a treatment for disorders or was administered for fewer than three consecutive cycles.

Data collection and analysis

Two authors abstracted and entered data into RevMan. We critically appraised the methodological quality of the included trials. For continuous variables, we computed the mean difference with 95% confidence interval (CI) using the random-effects model. For dichotomous variables, we calculated the risk ratio with 95% CI using the random-effects model.

Main results

We included one double-blind, double-dummy RCT comparing a quadriphasic oral contraceptive composed of dienogest and estradiol valerate with a monophasic oral contraceptive composed of levonorgestrel and ethinylestradiol. Contraceptive effectiveness, intracyclic bleeding and discontinuation due to side effectswere similar for quadriphasic andmonophasic pills. The number of women experiencing withdrawal bleeding was higher in the monophasic group compared to the quadriphasic group.Users of quadriphasic pills reported fewer bleeding/spotting days and fewer bleeding/spotting episodes than users of monophasic pills but the report did not specify whether

the bleeding/spotting was scheduled or unscheduled. More women using quadriphasic oral contraceptives reported breast pain compared to women using monophasic oral contraceptives.

Authors' conclusions

The available evidence is insufficient to determine whether quadriphasic differ from monophasic oral contraceptives in contraceptive effectiveness, bleeding pattern, minor side effects and acceptability. Studies that compare quadriphasic and monophasic oral contraceptives with an identical progestogen and estrogen type are needed to determine whether the quadriphasic approach differs from the monophasic approach. Studies that compare quadriphasic pills with monophasic pills containing 30 µg ethinylestradiol are indicated to determine whether quadriphasic oral contraceptives have an advantage over the current, first choice oral contraceptive. Until then, we recommend monophasic pills containing 30 µg estrogen as the first choice for women starting oral contraceptive use.

Plain language summary

Birth control pills with three phases versus one phase

Standard birth control pills contain two hormones: progestogen and estrogen. One-phase birth control pills contain the same dose of progestogen and estrogen every day. Four-phase birth control pills contain different amounts of progestogen and estrogen on different days. This review looked at how well one-phase birth control pills and four-phase birth control pills work to prevent pregnancy, how often they cause bleeding problems, how often users experience side effects and how many women stop using the pills.

We did a computer search for randomized controlled trials comparing four-phase birth control pills with one-phase birth control pills. We also wrote to researchers and makers of birth control pills to find other trials. Studies had to report on pregnancy, bleeding problems, side effects or stopping the use of pills. We did not include studies where the pills were used as a treatment for disorders like acne, hirsutism, polycystic ovary syndrome, bleeding problems or endometrioses, or where the pills were administered for less than three months. We assessed whether the studies were conducted properly.

We included one study comparing a four-phase pill composed of the progestogen dienogest and the estrogen estradiol valerate with an one-phase pill composed of the progestogen levonorgestrel and the estrogen ethinylestradiol. Four-phase birth control pills and onephase birth control pills had similar pregnancy rates. The number of women with blood loss in the period between two menstruations was similar for four-phase pills and one-phase pills. More women using one-phase birth control pills had a menstruation compared to women using four-phase birth control pills. The number of women who stopped using the pills because of side effects was similar for four-phase pills and one-phase pills. Breast pain was reported more frequently by women who used four-phase birth control pills than women who used one-phase birth control pills.

The presence of only one study made it impossible to adequately compare four-phase birth control pills with one-phase birth control pills. More studies are needed to determine whether four-phase pills have advantages over one-phase pills. Until then, we recommend one-phase pills containing 30 µg estrogen for women starting to use birth control pills.

Background

Since the introduction of combined oral contraceptives in the 1960s, the development of new hormonal contraceptives has focused on reducing the adverse effects while maintaining the benefits. Four approaches have been used to reduce the adverse effects of oral contraceptives and so increase compliance: (I) lowering of the steroid dose, (II) development of new steroids, (III) development of new formulas and schedules of administration, and (IV) development of new routes of administration.

Initially oral contraceptives contained a fixed dose of estrogen and progesterone for 21 days: so-called monophasic preparations. In order to provide better cycle control, biphasic and triphasic oral contraceptives were developed in the 1970s and 1980s (1). These preparations consist of two or three phases, each with a different progesterone dosage and in some preparations estrogen dosage. In the first phase progestogen levels are low, followed by a higher dose of the steroids in the second and third phases. To date, no benefits of the bi- and triphasic approach compared to the monophasic approach have been demonstrated (2;3).

Recently, the first quadriphasic oral contraceptive has been introduced. The rationale behind the development of the quadriphasic approach was to improve the unsatisfactory bleeding patterns observed with 17ß-estradiol-containing, mono- and biphasic oral contraceptives (4-6). Further, the quadriphasic approach is presented as more physiological since it mimics the natural cycle (7;8). Limited data are available on the contraceptive effectiveness, bleeding pattern and adverse effects of quadriphasic oral contraceptives.

Description of the intervention

Combined oral contraceptives consist of a progestogen component and an estrogen component. Monophasic preparations contain the same dose of progestogen and estrogen every day. In multiphasic oral contraceptives, the progestogen dosage, and in some preparations the estrogen dosage, varies over the cycle. Currently there is one quadriphasic preparation on the market. This oral contraceptive contains estradiol valerate 3 mg on days 1 and 2; dienogest 2 mg and estradiol valerate 2 mg on days 3 to 7; dienogest 3 mg and estradiol valerate 2 mg on days 8 to 24; estradiol valerate 1 mg on days 25 and 26; and placebo on days 27 and 28.

How the intervention might work

Combined oral contraceptives prevent ovulation by inhibiting gonadotropin secretion (1). Ovulation is primarily suppressed by the progestogen component, which prevents the LH-surge by inhibiting luteinizing hormone (LH) secretion. The estrogen component suppresses follicle-stimulating hormone (FSH) secretion but its major role is stabilizing the endometrium to minimize spotting and breakthrough bleeding. Other contraceptive effects of the progestogen component include thickening of the cervical mucus and altering the endometrium in a decidualized bed with atrophied glands.

Why it is important to do this review

Limited data are available on the contraceptive effectiveness, bleeding pattern and adverse effects of quadriphasic oral contraceptives. Suggested benefits of the quadriphasic oral contraceptive containing dienogest and 17ß-estradiol include better bleeding patterns and favorable effects on metabolic and hemostatic variables (4;9-11). However, disadvantages of quadriphasic oral contraceptives include a possible increased risk of pill-taking errors caused by the array of different color pills, complicated directions for catching up when a pill is missed, the higher price and potential inferiority in terms of side effects (7).

We systematically reviewed the literature to summarize the available evidence on the benefits and disadvantages of the quadriphasic approach. The results of the systematic review can assist healthcare providers in counseling women making contraceptive choices. A summary of the available evidence may also be useful for researchers in planning future studies.

Objectives

The aim of this review was to compare the contraceptive effectiveness, bleeding pattern, minor side effects and acceptability of quadriphasic oral contraceptive pills versus monophasic oral contraceptive pills.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials in any language. We excluded non-randomized trials.

Types of participants

We included all women of reproductive age enrolled in the randomized controlled trials. Eligibility criteria were those used by the researchers. We included women starting oral contraceptives as well as women switching oral contraceptives.

Types of interventions

Interventions included any quadriphasic oral contraceptive pill compared to any monophasic oral contraceptive pill when used to prevent pregnancy. We excluded studies where the intervention was primarily used as a treatment for disorders, e.g. acne, hirsutism, polycystic ovary syndrome, dysmenorrhea, menorrhagia or endometriosis. Interventions had to be applied for a minimum of three consecutive cycles to be eligible for inclusion.

Types of outcome measures

PRIMARY OUTCOMES

The main outcome was pregnancy. We did not include studies which focus on follicular growth or ovulation.

SECONDARY OUTCOMES

Other outcomes were bleeding patterns, minor side effects, ease of use and trial discontinuation. We excluded studies which primarily focus onmetabolic and hemostatic outcome measures. The definitions of bleeding indices were those specified by the authors.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE and POPLINE for publications comparing quadriphasic withmonophasic oral contraceptive pills. In addition, we searched for current trials through Clinical- Trials.gov and the International Clinical Trials Registry Platform (ICTRP). The search strategies are shown below.

MEDLINE

contraceptives, oral [mesh] AND (quadrophasic OR four phasic OR four-phasic OR quadri-step OR quadro-step OR quadro step OR "four phasic" OR four-phase OR "four phase" OR "dynamic dosing")

Limited to: humans, female, clinical trial, meta-analysis, randomized controlled trial, review, comparative study, controlled clinical trial, multicenter study

POPLINE

(oral contraceptive*/oral contraceptive agent*) & (quadriphasic/quadrophasic/four phasic/four-phasic/"quadri step"/quadri-step/"quadro step"/ quadro-step)

EMBASE

(oral contraceptive or oral contraceptive agent) and (quadriphasic or quadrophasic or four phasic or four-phasic or "quadri step" or quadri-step or "quadro step" or quadro-step)

CENTRAL

oral contraceptives and phasic

ClinicalTrials.gov

oral contraceptives and quadriphasic or quadrophasic or phasic or quadro-step or quadro step or step

ICTRP

oral contraceptives and quadriphasic

Searching other resources

We reviewed the reference lists of identified studies, review articles and book chapters for additional trials. We contacted the authors of the included trials and pharmaceutical companies marketing quadriphasic oral contraceptives to inquire whether they were aware of any published or unpublished studies which we have missed with our search.

Data collection and analysis

Selection of studies

One author assessed for inclusion or exclusion all titles and abstracts identified during the literature searches under unblinded conditions.

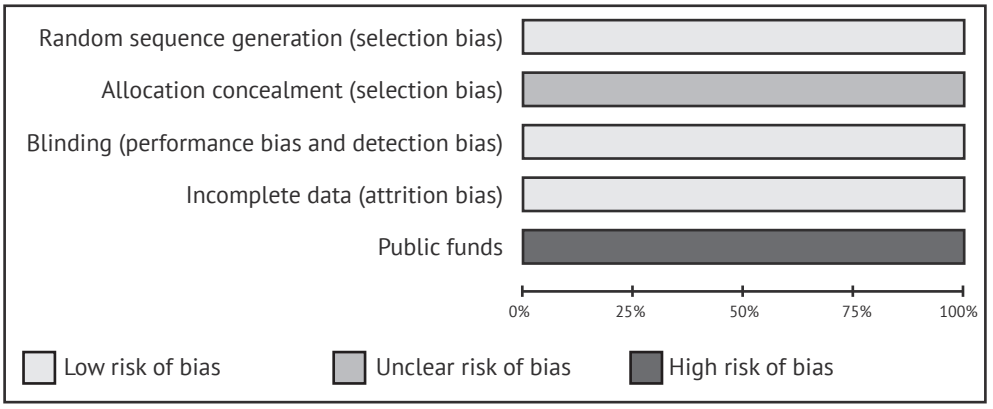
Data extraction and management

One author extracted the data from the included studies under unblinded conditions and entered the data into RevMan (12). In addition to the methodological quality of the study and outcome measures, we extracted data on participants, inclusion and exclusion criteria, study sites, duration of study, study medication, method of collecting the data and funding source. Another author performed a second, independent data abstraction and verified the correct entry of the data. No disagreements about the extracted and entered data occurred.

Assessment of risk of bias in included studies

We critically appraised the methodological quality of the trials according to the recommended principles described in the Cochrane Handbook (13). We focused on the method of generating the allocation sequence, the use and method of allocation concealment, the use and method of blinding, exclusion of participants after randomization, discontinuation and loss to follow-up. Limitations in study design are presented in Risk of bias in included studies, Characteristics of included studies, Figure 1 and Figure 2, and are discussed in the Quality of the evidence section.

Figure 1. *Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.*



Dealing with missing data

We contacted the authors of the eligible and possibly eligible trials for additional information about the study methods and the various outcome measures.

Assessment of heterogeneity

Since only one study was eligible for inclusion we could not assess heterogeneity by the Chi^2 test or assess the impact on the meta analysis using the I^2 statistic.

Data synthesis

We compared the contraceptive effectiveness, bleeding patterns, minor side effects and trial discontinuation between quadriphasic oral contraceptives and monophasic oral contraceptives. The included study reported the number of women who became pregnant, the mean number of bleeding/spotting days with standard deviation, the mean number of bleeding/spotting episodes with standard deviation, the number of women discontinuing early due to side effects and the number of women reporting a particular adverse effect. In addition, the authors provided us the number of women with intracyclic bleeding and the number of women with withdrawal bleeding per cycle. No data on ease of use were mentioned in the paper or provided by the authors. For continuous variables, we computed the mean difference with 95% confidence interval using the random-effects model. For dichotomous variables, we calculated the risk ratio with 95% confidence interval using the random-effects model.

Subgroup analysis and investigation of heterogeneity

Since only one study was included we could not conduct a subgroup analysis by examining only studies with high methodological quality, i.e. studies with an adequate method of generating the allocation sequence, an adequate method of allocation concealment, an adequate method of

blinding and less than 20% loss to follow-up. A subgroup analysis including only starters/switchers was also not performed because the outcomes were not reported according to whether the woman was a starter or switcher.

Results

Description of studies

See: Characteristics of included studies.

Results of the search

The search strategy yielded 31 papers. Four studies were nonrandomized. Twenty-six studies did not meet our inclusion criteria or focused on outcomes not included in this review.

Included studies

One study met the inclusion criteria for this review (A). The study compared a quadriphasic oral contraceptive composed of estradiol valerate 3 mg on days 1 and 2; dienogest 2 mg and estradiol valerate 2 mg on days 3 to 7; dienogest 3 mg and estradiol valerate 2 mg on days 8 to 24; estradiol valerate 1 mg on days 25 and 26; and placebo on days 27 and 28, with a monophasic oral contraceptive composed of levonorgestrel 100 µg and ethinylestradiol 20 µg on days 1 to 21 and placebo on days 22 to 28. The trial included 804 randomized women of whom 402 were allocated to the quadriphasic group and 402 to the monophasic group. The study lasted seven cycles and included 20 822 womenyears. The main objective of the study was to compare bleeding pattern and cycle control with the two preparations. Secondary outcome measures were the number of unintended pregnancies, satisfaction with the treatment and safety. Detailed information regarding participants, inclusion and exclusion criteria, study sites, duration of study, study medication and outcome measures is presented in the Characteristics of included studies.

Excluded studies

There are no excluded studies.

Risk of bias in included studies

Allocation

Randomization was done by a computer-generated random allocation sequence generated at the sponsor's central randomization service. The study did not report the use and method of concealing the treatment allocation sequence. Communication with the authors revealed no extra information.

Blinding

The study is described as a double-blind, double-dummy trial. The paper does not specify who was kept unaware of the oral contraceptives assigned and does not provide information regarding successful implementation of blinding. Communication with the authors revealed no extra information.

Incomplete outcome data

The study reported detailed information on number and reasons for discontinuation. Of the 402 women in the quadriphasic group, 37 women (9%) discontinued early, as did 40 women (10%) of the 402 women in the monophasic group. Three women in both groups did not receive the oral contraceptives after randomization. Fourteen women in the quadriphasic and 15 women in the monophasic group were withdrawn because of protocol violations. No women were lost to follow-up. Communication with the authors indicated analysis according to the intention-to-treat principle without further specification.

Other potential sources of bias

Funding

The trial was supported by the manufacturer of the studied quadriphasic and monophasic pills.

Effects of interventions

Contraceptive effectiveness

No significant difference in contraceptive effectiveness was observed between the quadriphasic and monophasic pills (Analysis 1.1). The study describes one unintended pregnancy caused by a method failure in the monophasic group.

Cycle control and bleeding pattern

Intracyclic bleeding

Additional data on intracyclic bleeding was provided by the authors. Overall, the number of women experiencing intracyclic bleeding did not differ between the quadriphasic and monophasic preparation (Analysis 1.2 to Analysis 1.15). During the fourth cycle the proportion of women having intracyclic bleeding was higher in the quadriphasic group compared to the monophasic group (risk ratio (RR) 1.45; 95% confidence interval (CI) 1.01 to 2.10).

Withdrawal bleeding

Data on withdrawal bleeding not described in the paper were provided by the authors. During each treatment cycle the proportion of women with withdrawal bleeding was higher in the monophasic group compared to the quadriphasic group (Analysis 1.16 to Analysis 1.22 and Figure 2;

at cycle 3 RR 0.88; 95% CI 0.83 to 0.93; at cycle 6 RR 0.89; 95%CI 0.84 to 0.94). Further, the paper describes that the duration and intensity of withdrawal bleeding was shorter and lighter in women using quadriphasic oral contraceptives compared to women using monophasic oral contraceptives. The median length of withdrawal bleeding was 4.0 days for users of quadriphasic pills versus 5.0 days for users of monophasic pills (reported P < 0.05). Themedian intensity score of withdrawal bleeding was 3 (light) for women using quadriphasic oral contraceptives compared to 4 (normal) for women using monophasic oral contraceptives.

Spotting/bleeding

Women using quadriphasic oral contraceptives reported fewer bleeding/spotting days (Analysis 1.23; Analysis 1.24; Figure 3; reference period one mean difference (MD) -4.20; 95%CI -5.52 to -2.88; reference period twoMD-2.50; 95%CI -3.65 to -1.35) and fewer bleeding/spotting episodes (Analysis 1.25; Analysis 1.26; Figure 4; reference period one MD -0.40; 95% CI -0.56 to - 0.24 reference period two MD -0.10; 95% CI -0.26 to 0.06) than women using monophasic oral contraceptives. The report did not specify whether the bleeding/spotting was scheduled or unscheduled.

Discontinuation

The number of women who discontinued due to adverse effects did not differ between quadriphasic and monophasic oral contraceptives (Analysis 1.27). No discontinuations because of bleeding disorders occurred.

Side effects

During the study period significantly more women using quadriphasic oral contraceptives reported breast pain compared to women using monophasic oral contraceptives (Analysis 1.30; Figure 5; RR 3.25; 95% CI 1.07 to 9.88). The number of women reporting headache, acne, alopecia, migraine and increase in body weight did not differ between the two preparations (Analysis 1.28; Analysis 1.29; Analysis 1.31 to Analysis 1.35).

Discussion

Summary of main results

We identified only one trial including 804 women which compared a quadriphasic oral contraceptive composed of estradiol valerate 3 mg on days 1 and 2; dienogest 2 mg and estradiol valerate 2 mg on days 3 to 7; dienogest 3 mg and estradiol valerate 2 mg on days 8 to 24; estradiol valerate 1mg on days 25 and 26; and placebo on days 27 and 28, with a monophasic oral contraceptive composed of levonorgestrel 100 µg and ethinylestradiol 20 µg on days 1 to 21 and placebo on days 22 to 28 (A).

The outcomes were contraceptive effectiveness, bleeding pattern, side effects and discontinuation due to side effects. Users of quadriphasic oral contraceptives were less likely to experience a withdrawal bleeding compared to users of monophasic oral contraceptives. Additionally, the duration and intensity of the withdrawal bleeding was lower in the group of women using quadriphasic oral contraceptives. In the group of quadriphasic pill users more women reported breast pain compared to the group of monophasic pill users. The contraceptive effectiveness, intracyclic bleeding and discontinuation due to side effects did not differ between the two groups.

Overall completeness and applicability of evidence

The presence of only one study including 804 women for seven treatment cycles made it impossible to adequately compare the quadriphasic approach with the monophasic approach in terms of contraceptive effectiveness, bleeding pattern, side effects and discontinuation due to side effects. The two studied preparations differed in progestogen and estrogen content. Since the progestogen as well as the estrogen type is thought to affect cycle control, the observed differences in bleeding pattern might be (partially) explained by the differences in progestogen and estrogen type rather than the phasic approach. In addition, the quadriphasic oral contraceptive was compared with a monophasic oral contraceptive containing 20 µg ethinylestradiol. Contraceptive pills containing 20 µg ethinylestradiol have been shown to result inmore bleeding disturbances and discontinuation due to side effects than contraceptive pills containing more than 20 µg ethinylestradiol (14).

Quality of the evidence

The study featured an adequate method of generating a random allocation sequence, was reported to be double-blinded and had low discontinuation rates. Limitations of the methodological quality of the trial included no description of the use or method of allocation concealment, no specification of who was kept unaware of the assigned treatment, exclusion of participants after randomization and funding of the trial by the manufacturer of the quadriphasic pill. Inadequate methods of allocation concealment and exclusion of participants after randomization may lead to bias (15;16). Studies sponsored by pharmaceutical companies are more likely to have outcomes favoring the sponsor than studies funded by other sources (17;18).

Potential biases in the review process

No potential biases in the review process were evident.

Agreements and disagreements with other studies or reviews

Beside the included randomized controlled trial, two multicentre, non-comparative trials assessing the contraceptive effectiveness, bleeding pattern, minor side effects, early discontinuation and satisfaction during use of the quadriphasic dienogest/estradiol valerate oral contraceptive have been conducted (19;20). Both studies were funded by the manufacturer of the quadriphasic pill. One study has been published in a peer-reviewed journal (20). In this study 13 pregnancies occurred during 23,368 cycles of quadriphasic dienogest/estradiol valerate use (Pearl Index 0.73). No data on bleeding pattern were reported. The paper describes that 272 of the 1377 users of the dienogest/estradiol valerate oral contraceptive (19.8%) reported adverse effects related to the treatment; breast pain was most commonly mentioned (50 users; 3.6%). During the study 140 participants (10.2%) discontinued early due to adverse effects. All reviews, which are narrative, rely on the included randomized trial and the two non-comparative trials (4-6).

Author's conclusions

Implications for practice

We recommend monophasic oral contraceptives as the first choice for women starting oral contraceptive use, given the absence of proven advantages of the quadriphasic approach, the greater complexity of quadriphasic pill regimens, the higher costs of quadriphasic oral contraceptives and the sparse experience with quadriphasic pills. At first prescription, monophasic pills containing 30 µg estrogen are preferred over monophasic pills containing 20 µg since the latter cause more bleeding disturbances and discontinuation (14). Women experiencing heavy menstrual bleeding may benefit from quadriphasic oral contraceptives but continuous use of a monophasic oral contraceptive to avoid menstrual bleeding may also be an alternative.

Implications for research

All new contraceptive preparations require comparison of contraceptive effectiveness, bleeding pattern, side effects, discontinuation rates and beneficial effects with a gold standard in large, adequately reported, high-quality, randomized controlled trials. Studies that compare quadriphasic and monophasic oral contraceptives with an identical progestogen and estrogen type are needed to determine whether the quadriphasic approach differs from the monophasic approach. Trials that compare quadriphasic pills with monophasic pills containing 30 µg ethinylestradiol are indicated to determine whether quadriphasic oral contraceptives have an advantage over currently and widely used oral contraceptives with which providers and consumers have extensive experience.

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** Indicates the major publication for the study*

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Ahrendt 2009

Methods	Double-blind randomized controlled trial
Participants	846 women at 34 sites in Europe Inclusion criteria were healthy women aged 18 to 50 years Exclusion criteria were pregnancy; lactation; fewer than 3 menstrual cycles following childbirth, abortion or lactation; current use of an IUD; BMI more than 30 kg/m2; use of long-acting progestins within 6 months prior to the study entry; hypersensitivity to study drug ingredients; known or suspected malignant or pre-malignant disease; more than 10 cigarettes per day when aged 18 to 30 years or smoking when aged older than 30 years; use of other sex steroids Starters and switchers were included in the study
Interventions	Quadriphasic dienogest/estradiol valerate (E2V 3 mg on days 1 and 2, DNG 2 mg and E2V 2 mg on days 3 to 7, DNG 3 mg and E2V 2 mg on days 8 to 24, E2V 1 mg on days 25 and 26 and placebo on days 27 and 28) versus monophasic levonorgestrel/ethinylestradiol (LNG 100 µg and 20 µg EE on days 1 to 21 and placebo on days 22 to 28). Women were instructed to take the tablets at the same time each day and to take any missed tablets as soon as remembered. If the interval between taking two consecutive tablets was more than 36 hours a non-hormonal contraceptive had to be used
Outcomes	The primary outcome measures are cycle control and bleeding patterns Secondary outcomemeasures include the number of unintended pregnancies, satisfaction with treatment and safety Scheduled bleeding was defined as a bleeding or spotting episode that began during the hormone-free period or started not more than 4 days before the progestin withdrawal in any cycle that continued through into the progestin-free interval. Absence of scheduled bleeding was defined as no bleeding until day 20 of consecutive cycles with the quadriphasic preparation and day 17 with the monophasic preparation Unscheduled bleeding was defined as all other bleeding episodes A bleeding/spotting episode was defined bleeding/spotting days bounded on either end by equal or more than 2 days of no bleeding/spotting Use of daily diary cards to collect data on pill intake and cycle control. Data on side effects were recorded if reported spontaneously
Notes	The report does not provide an a priori hypothesis. The report states a sample size which was chosen to obtain an acceptable estimate of the number of women required to permit acceptably precise comparisons between groups for the number of bleeding/spotting days per reference period. Study duration: 7 cycles

Risk of bias		
Bias	*Authors' judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low risk	Randomization by a computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	The use of allocation concealment is not described. Communication with the authors revealed no extra information
Blinding (performance bias and detection bias) All outcomes	Low risk	The study is reported as a double-blind, double-dummy trial. Who was kept unaware of the oral contraceptives assigned is not described. Communication with the authors revealed no extra information
Incomplete outcome data (attrition bias) All outcomes	Low risk	37 women in the quadriphasic group and 40 women in the monophasic group discontinued early. The reasons for discontinuation are described. 3 women in each group did not receive the oral contraceptives. No women were lost to follow-up. 14 women in the quadriphasic and 15 women in the monophasic group were withdrawn because of protocol violations. Unclear whether the analysis was according to the intention-to-treat principle. Communication with the authors indicated an analysis according to intention-to-treat without further specification
Public funds	High risk	The trial was supported by the manufacturer of the studied quadriphasic and monophasic pills

BMI: body mass index; DNG: dienogest; E2V: estradiol valerate; EE: ethinylestradiol; IUD: intrauterine device; LNG: levonorgestrel

Data and analyses

Comparison 1. *3 mg E2V on days 1-2; 2 mg DNG/2 mg E2V on days 3-7; 3 mg DNG/2 mg E2V on days 8-24; 1 mg E2V on days 25-26; and placebo on days 27-28 versus 100 µg LNG/20 µg EE on days 1-21 and placebo on days 22-28*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy	1	798	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.16]
2 Proportion of women with intracyclic bleeding at cycle 1	1	784	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.81, 1.47]
3 Proportion of women with intracyclic bleeding at cycle 2	1	780	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.97, 1.97]
4 Proportion of women with intracyclic bleeding at cycle 3	1	773	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.64, 1.31]
5 Proportion of women with intracyclic bleeding at cycle 4	1	762	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.01, 2.10]
6 Proportion of women with intracyclic bleeding at cycle 5	1	748	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.70, 1.61]
7 Proportion of women with intracyclic bleeding at cycle 6	1	746	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.69, 1.62]
8 Proportion of women with intracyclic bleeding at cycle 7	1	743	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.84, 1.88]
9 Number of intracyclic bleeding episodes at cycle 1	1	784	Mean Difference (IV, Random, 95% CI)	0.0 [-0.07, 0.07]
10 Number of intracyclic bleeding episodes at cycle 2	1	780	Mean Difference (IV, Random, 95% CI)	0.1 [0.04, 0.16]
11 Number of intracyclic bleeding episodes at cycle 3	1	773	Mean Difference (IV, Random, 95% CI)	0.0 [-0.06, 0.06]
12 Number of intracyclic bleeding episodes at cycle 4	1	762	Mean Difference (IV, Random, 95% CI)	0.1 [0.04, 0.16]
13 Number of intracyclic bleeding episodes at cycle 5	1	748	Mean Difference (IV, Random, 95% CI)	0.0 [-0.06, 0.06]
14 Number of intracyclic bleeding episodes at cycle 6	1	746	Mean Difference (IV, Random, 95% CI)	0.0 [-0.05, 0.05]
15 Number of intracyclic bleeding episodes at cycle 7	1	743	Mean Difference (IV, Random, 95% CI)	0.0 [-0.05, 0.05]
16 Proportion of women with withdrawal bleeding at cycle 1	1	784	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.83, 0.94]
17 Proportion of women with withdrawal bleeding at cycle 2	1	780	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.79, 0.89]
18 Proportion of women with withdrawal bleeding at cycle 3	1	773	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.83, 0.93]
19 Proportion of women with withdrawal bleeding at cycle 4	1	762	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.85, 0.95]
20 Proportion of women with withdrawal bleeding at cycle 5	1	748	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.81, 0.92]

21 Proportion of women with withdrawal bleeding at cycle 6	1	746	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.84, 0.94]
22 Proportion of women with withdrawal bleeding at cycle 7	1	743	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.82, 0.92]
23 Number of bleeding/spotting days in reference period 1	1	798	Mean Difference (IV, Random, 95% CI)	-4.20 [-5.52, -2.88]
24 Number of bleeding/spotting days in reference period 2	1	798	Mean Difference (IV, Random, 95% CI)	-2.5 [-3.65, -1.35]
25 Number of bleeding/spotting episodes in reference period 1	1	798	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.56, -0.24]
26 Number of bleeding/spotting episodes in reference period 2	1	798	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.26, 0.06]
27 Number of women discontinuing due to adverse effects	1	798	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.47, 2.13]
28 Number of women reporting an adverse event	1	798	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.84, 1.34]
29 Number of reported adverse events per total number of women	1	798	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.28]
30 Number of women reporting breast pain	1	798	Risk Ratio (M-H, Random, 95% CI)	3.25 [1.07, 9.88]
31 Number of women reporting acne	1	798	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.19, 1.64]
32 Number of women reporting migraine	1	798	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.08, 2.05]
33 Number of women reporting headache	1	798	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.35, 2.82]
34 Number of women reporting alopecia	1	798	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.17, 3.33]
35 Number of women reporting increase in body weight	1	798	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.09, 2.71]