TRIPHASIC COMBINATION OF ETHINYL ESTRADIOL AND GESTODENE

LONG-TERM CLINICAL TRIAL

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Abstract

A triphasic oral contraceptive containing ethinyl estradiol and gestodene was used by 1933 women for up to 36 cycles in order to evaluate contraceptive efficacy, general tolerance and cycle control. Altogether, 30,763 treatment cycles were recorded.

Two pregnancies were seen, both of them classified as user failure. The rates of spotting and breakthrough bleeding fell below the rates of the pre-treatment cycle after the first three months of treatment. Adverse events were mostly minor with breast tension and headaches the most common complaints. After the first three cycles, the incidence of most complaints was the same as or even lower than in the pre-treatment cycle. Blood pressure and body weight remained practically unchanged.

The trial preparation provided reliable contraception with good general tolerance and cycle control when taken for up to three years.

Introduction

Combined oral contraceptive pills are the most reliable reversible method of contraception. It is however important in a preparation which is given daily to healthy women - often over several years - that these oral contraceptives have little or no effect on anything else but reproductive function. In the "older" progestogens deriving from 19-nor-testosterone, residual androgenic effects on lipoprotein patterns have been found.

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Although these effects on lipid metabolism are usually well within the normal range and no long-term clinical effects have been detected in large-scale trials, research in oral contraceptives in the last years has focussed mainly on finding new progestogens (gonanes) which have minimal impact on metabolic parameters.

One of the "new generation" of progestogens is gestodene which, as the progestogen compound in a monophasic oral contraceptive, has been marketed in several countries in Europe (trade names include Femovan®, Femodene®, Gynera®, Ginoden®). This oral contraceptive containing gestodene as the progestogen component has been shown to have a strong anti-gonadotrophic effect, no residual androgenic effects on lipid metabolism, and excellent contraceptive reliability with good clinical tolerance.

In the trial reported here, gestodene was combined with ethinyl estradiol for a triphasic oral contraceptive (SH D 415 G). Data on 24 treatment cycles have already been published. The triphasic principle provides a slightly higher estrogen dose in the critical mid-cycle period while increasing the progestogen dosage progressively towards the end of the cycle, thereby imitating the natural hormone levels in the normal menstrual cycle.

Methods

Trial design

This trial was designed as a large-scale, multicentre trial; 123 investigators in 11 countries (Argentina, Austria, Belgium, France, Germany, Great Britain, Italy, Portugal, The Netherlands, Uruguay, and Venezuela) took part in the trial.

Every six months on the occasion of the follow-up visit, the volunteers were asked if they wanted to continue taking part in the trial. The aim was to document at least 20,000 cycles over a period of three years; therefore, 2000 women were recruited.

Trial preparation

SH D 415 G is a triphasic oral contraceptive containing ethinyl estradiol (EE) and gestodene (GES). The composition is:

- 6 coated tablets containing 0.03 mg EE + 0.05 mg GES
- 5 coated tablets containing 0.04 mg EE + 0.07 mg GES
- 10 coated tablets containing 0.03 mg EE + 0.10 mg GES
**Trial population**

Women were included in the trial with no upper age limit if they had no contraindications for oral contraceptive use.

Two-thousand-one women were recruited; 68 women were excluded from the analysis for the following reasons:

- 58 women did not start taking the trial preparation, so only the pre-treatment values were available.
- 9 cases could not be evaluated because of incomplete documentation in the case record forms.
- One woman had hepatopathy before the start of the trial which was not in accordance with the inclusion criteria.

Therefore, 1933 women were treated with the trial preparation, comprising 30,763 treatment cycles.

Three-hundred-thirty-four women (17.28%) were less than 20 years old, 1077 women (55.72%) were between 20 and 30, 450 (23.28%) were between 30 and 40, and 72 women (3.72%) between 40 and 50 years old. Women over 50 did not take part in this trial.

One thousand one hundred ninety-one women (61.8%) were non-smokers. The majority of the rest were moderate smokers, with only 27 women (1.4%) admitting to smoking more than 20 cigarettes per day.

**Investigation parameters**

Before the start of the trial, a general history with special attention to thrombophlebitic or thromboembolic events in the past was taken. Informed consent was obtained from all participants and a general and gynaecological examination was performed. The following parameters were assessed before entry into the trial and subsequently at regular intervals (if possible every month):

- bleeding patterns
- weight
- blood pressure
- general well-being and complaints
Results

Contraceptive efficacy

Despite several mistakes in pill intake (on average, 2.5% of all women forgot to take one or more pills per cycle, the percentage ranging from 1.5% to 4%), only two women became pregnant. One of these women forgot two consecutive pills in the first intake cycle, the other woman took a long-term concomitant medication which contained a barbiturate. Barbiturates are thought to interact with contraceptive steroids by inducing hepatic enzymes. Therefore, both pregnancies can be attributed to user failure or interaction rather than to method failure. The uncorrected Pearl Index in this trial is 0.09.

Bleeding patterns

Figures 1 - 3 show the changes in spotting (very slight intermenstrual bleeding necessitating no sanitary protection), breakthrough bleeding (intermenstrual bleeding where any form of sanitary protection was used) and dysmenorrhoea during the trial.

Spotting and breakthrough bleeding, as expected, showed a higher incidence in the first three treatment cycles as compared to the pre-treatment cycle. Subsequently the incidence of both spotting and breakthrough bleeding decreased to values below those of the pre-treatment cycle as can be seen in the figures. The higher percentage values of spotting in the later cycles (30-36) probably result from bias due to the lower number of participants.

Figure 1: Spotting
Dysmenorrhoea showed a distinct decrease under treatment. The incidence of mild dysmenorrhoea was 20% of all women in the pre-treatment cycle. After the first few cycles, less than 4% of the women reported dysmenorrhoea. The rate of severe dysmenorrhoea dropped from almost 5% before treatment to less than 0.5% during pill intake.
Tolerance

The overall tolerance of the trial preparation was good. Objective adverse events were rare, in fact the incidence of acne, chloasma and edema decreased in the trial period as compared to the pre-treatment cycle. Four women had thrombotic or thrombophlebitic events. Out of these, one was a case of stroke in a 46-year-old woman with pre-existing unstable hypertension and hyperlipidaemia who was included in violation of the trial protocol. Another case was a post-operative pulmonary embolism after emergency appendectomy. A third case was local thrombophlebitis after joint surgery and in the fourth case no predisposing factors could be found although a coagulation disorder cannot be ruled out because the volunteer did not return for further investigation. So-called hepatopathy (classified thus in the case record forms but on inquiry discovered to be mostly benign abdominal discomfort or transient increase in hepatic enzymes) was found in five women (0.25%) and constituted the reason for dropout in three cases.

Figure 4 shows the incidence of acne (the most commonly reported objective symptom) in detail. It is perhaps noteworthy that acne was reduced by more than half after the first months of treatment.

![Figure 4: Acne](image)

Regarding the subjective symptoms, breast tension and headache were the most commonly mentioned symptoms.

Figures 5 and 6 show the incidence of breast tension and headache per cycle. About 7% of all women complained of breast tension in the pretreatment cycle, and only in the first three treatment cycles higher incidences were found, as can be seen in Figure 5.
When the percentage of women complaining of headache is shown per cycle, one can see that regardless of pill intake, between 3% and 8.3% of all women had a headache in any given cycle. No increase is seen with the treatment drug as compared to the pre-treatment cycle - except for the first three treatment cycles (see Figure 6 for details).
Reasons for dropping out

Two women (0.1%) had to leave the trial because of pregnancy (see above), 249 women (12.9%) dropped out of the trial because of adverse events, 424 (21.9%) left the trial because of private reasons, e.g. wish to become pregnant. Nine-hundred-eighty women finished the trial voluntarily after one of the six-monthly follow-up appointments as provided for in the protocol. A further 278 women took the trial preparation for the full 36 months.

The adverse events stated most often as a reason for dropping out were:

- intermenstrual bleeding in 61 cases (3.26% of all women)
- headache in 44 cases (2.28%)
- breast tension in 39 cases (2.02%)
- nausea in 29 cases (1.5%)
- migraine in 24 cases (1.24%)
- weight gain in 21 cases (1.09%)
- vomiting in 15 cases (0.78%)
- varices discomfort in 13 cases (0.67%)
- dizziness in 11 cases (0.57%) and
- decrease of libido in 10 cases (0.52%)

Most of the women who dropped out of the trial because of adverse events did so in the first months:

Cycle 1-6: 158 women
Cycle 7-12: 47 women
Cycle 13-18: 28 women
Cycle 19-24: 10 women
Cycle 25-30: 4 women
Cycle 31-36: 2 women

Discussion

In this large-scale trial over up to 36 cycles, SH D 415 G has shown to be reliable as regards contraceptive efficacy with an uncorrected Pearl Index of 0.09, both pregnancies being classified as user failure.

The preparation showed good cycle control with rates of spotting and breakthrough bleeding which, after the first few months of intake, were below the rates seen in the pre-treatment cycle.

12.9% of the participants dropped out of the trial because of adverse events, mostly the well-known adjustment difficulties in the first few cycles: symptoms such as intermenstrual bleeding, headache or breast tension. This rate is well within the range of what would be expected in a clinical trial of this type. The preparation showed a beneficial effect on the incidence of acne.
In conclusion, SH D 415 G is a well-tolerated oral contraceptive with a low rate of intermenstrual bleeding, after the first few intake cycles, which provides reliable contraceptive protection.

References


