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**Is The Combined Oral Contraceptive Treatment Of 150 mcg
Levonorgestrel And 30 mcg Ethinyl Estradiol Effective In
Preventing Bothersome Unscheduled Uterine Bleeding?**

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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ABSTRACT

Objective: The objective of this selective evidence-based medicine (EBM) review is to determine whether or not the combined oral contraceptive treatment of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol is effective in preventing unscheduled uterine bleeding.

Study Design: Review of two randomized controlled trials (RCTs) and one post hoc analysis, published after 2014 all in the English language.

Data Sources: Two randomized controlled trials (RCTs) and one post hoc analysis, all of which evaluate the efficacy of the combined oral contraceptive (COC) treatment of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol in preventing bothersome unscheduled uterine bleeding. In both RCTs, an experimental group is compared to a control group receiving an identical appearing placebo. All studies were found using PubMed.

Outcomes Measured: Each of the three articles analyzed the effects of the combined oral contraceptive of levonorgestrel and ethinyl estradiol in preventing bothersome unscheduled uterine bleeding. A five-point Likert Scale and bleeding diaries were the methods used to measure bothersome unscheduled uterine bleeding.

Results: In the studies by Guiahi et al.² and Hou et al.⁶, participants receiving the treatment of combined oral contraceptive showed statistically significant reduction in unscheduled uterine bleeding compared to the control group with p-values of <0.01 (Guiahi) and 0.03 (Hou). The study by Nappi et al.⁷ compared participants with 0-6 and >6 days of bleeding and showed significant improvement that increased each 91-day cycle of the combined oral contraceptive treatment with a confidence interval of 95% and an odds ratio (OR) of 1.531.

Conclusions: Based on the systematic review of the two randomized controlled trials and one post hoc analysis, one can decisively say that 150 mcg levonorgestrel and 30 mcg ethinyl estradiol is effective in treating bothersome unscheduled uterine bleeding. All three studies verified statistically significant reduction in bleeding with use of the therapy.

Keywords: Combined oral contraceptive, uterine bleeding, levonorgestrel, ethinyl estradiol, and unscheduled bleeding.

INTRODUCTION

Unscheduled uterine bleeding is defined as any bleeding that occurs while using active contraceptive hormones, excluding bleeding that begins in the hormone-free interval and continues through days one to four of the subsequent active cycle.¹ A common reason why women often choose to discontinue hormonal contraception is dissatisfaction with its effects of uterine bleeding. Interventions that prevent or treat unscheduled bleeding could improve contraceptive acceptability and increase compliance, thus leading to fewer unplanned pregnancies.¹

In clinical trials, up to 11.3% of women report discontinuation of contraceptives for bothersome bleeding that is ultimately considered unacceptable.² The bleeding pattern most bothersome to women is unscheduled bleeding or spotting and can occur with all hormonal methods of contraception.¹ Prior to initiation of a contraceptive, healthcare providers should thoroughly counsel women about the range of bleeding patterns associated with its use. Providing this education will increase adherence to the method of contraception and reassure women that if used as directed, unscheduled uterine bleeding does not mean the method is ineffective at preventing pregnancy.¹ However, proper adherence to the method of contraception does not ensure that bothersome unscheduled uterine bleeding will not continue to occur, causing women to seek treatment from their healthcare provider.

Seeking a prescribed form of contraceptive requires a minimum of one annual visit for initiation or maintenance of the contraception.³ Women should be instructed by their provider to follow up at any point to discuss side effects or complications. A complication such as unscheduled bleeding will increase the number of required annual visits for women who seek treatment.³ There are large differences in cost between different methods of hormonal contraception, with prescription contraceptives being the most expensive due to requiring

medical supervision.⁴ Implants, such as Nexplanon, cost over \$800 each.⁵ Intrauterine devices, such as the Mirena and ParaGard, cost over \$1,000 each. The cost of birth control pills is around \$20 to \$50 per pack with monthly purchases adding up to a yearly sum of \$240 to \$600. The Depo-Provera shot is \$60 each with a total of around \$240 per year. NuvaRing totals to approximately \$1,000 per year.⁵ Since all methods of contraception can result in unscheduled bleeding, birth control pills are by far one of the most cost-effective options for women seeking treatment.^{1,5}

The pathogenesis of unscheduled bleeding in women using hormonal contraception is poorly understood.¹ Unscheduled uterine bleeding is thought to be due to a relatively thick endometrium transitioning to a relatively thin endometrium as a result of the progestin-dominant component of all hormonal contraceptives.¹ Many women find it acceptable to wait for spontaneous resolution of the problem. For those women who seek an intervention, a monophasic low-dose combined oral contraceptive (COC) is prescribed. Currently there is no data supporting one low dose COC over another for this indication.^{1,2} However, COCs are shown to effectively interrupt unscheduled uterine bleeding during treatment.^{1,2} This paper focuses on two randomized controlled trials (RCTs) and one post hoc analysis to evaluate the efficacy of a combined oral contraceptive treatment to prevent unscheduled uterine bleeding.

OBJECTIVE

The objective of this selective evidence-based medicine review is to determine whether or not the combined oral contraceptive treatment of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol is effective in preventing unscheduled uterine bleeding.

METHODS

The studies used in this systematic review included two randomized controlled trials that were both double-blind and placebo-controlled, and one post hoc analysis. The population studied includes women seeking intervention for complaints of bothersome unscheduled uterine bleeding or bleeding irregularity unrelated to an anatomical or organic source. The intervention used in each study is a combined oral contraceptive of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol. Each of the randomized controlled trials utilized an experimental group receiving an identical appearing placebo as the comparison to the intervention. The post hoc analysis compared participants who experienced 0-6 days and >6 days of bleeding with each 91-day cycle of the treatment. The outcome measured in each study includes the efficacy of the intervention in providing improvement of unscheduled uterine bleeding.

All studies were discovered in the PubMed database using the key words “combined oral contraceptive,” “uterine bleeding,” “levonorgestrel and ethinyl estradiol,” and “unscheduled bleeding.” Each article was published in the English language and in peer-reviewed journals. Articles were selected based on their relevance to the clinical question and if they included patient-oriented evidence that matters (POEMS). Inclusion criteria included studies that were randomized, controlled, and double-blind. Exclusion criteria included studies dated prior to 2007, studies with women under the age of fourteen, and studies with women who were not experiencing uncontrolled bothersome uterine bleeding. Statistics reported in this review include number needed to treat (NNT), p-values, control event rate (CER), experimental event rate (EER), relative risk reduction (RRR), absolute risk reduction (ARR), odds ratio (OR), and confidence interval (CI). The demographics and characteristics specific to each study can be found in Table 1.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# PTs	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Guiahi ² (2015)	RCT	32	18-44	Women who were English or Spanish speaking with a bleeding episode of at least 7 consecutive days at the time of enrollment	Women category 3-4 for estrogen therapy, BMI >35, BP >135/85 mmHg on more than 2 occasions, +pregnancy test, +chlamydia test, unable to swallow pills, severe medical conditions, taking hepatic enzyme inducing medications, allergy to COC, anatomic source of bleeding	0	Levonorgestrel 150 mcg and Ethinyl Estradiol 30 mcg for 14 days
Hou ⁶ (2016)	RCT	26	17-34	Women over the age of 14 who had requested intervention for complaints of significant bleeding irregularity or heavy flow.	Women category 3-4 for estrogen, previous treatment for bleeding with an etonogestrel implant, orthostatic vitals, organic causes for the bleeding	2	Levonorgestrel 150 mcg and Ethinyl Estradiol 30 mcg for 28 days
Nappi ⁷ (2017)	Post hoc analysis	799	18-40	Sexually active adult women seeking COC as primary birth control, switching from another COC regimen, no prior history of COC use, women without any COC use in the last 6 months	Active smokers who were older than 35.	112	Levonorgestrel 150 mcg and Ethinyl Estradiol 30 mcg in 91- day cycles over 1- year low dose ethinyl estradiol in replacement of the normal 7- day hormone free period

OUTCOMES MEASURED

The outcome measured in each of the studies was the amount of bleeding experienced by the participants both in the experimental and control groups. Guiahi et al. measured bleeding by having participants complete a bleeding and pill-taking diary.² In the diary, participants recorded if the pill was taken on the appropriate day, the time the pill was taken each day, and the amount of bleeding experienced on a scale of none, spotting, light, normal or heavy.² Hou et al. reported changes in bleeding during the last week of the study using a 5-point Likert scale.⁶ The scale included bleeding that improved significantly, improved slightly, no change, worsened slightly, or worsened significantly.⁶ Nappi et al. required participants to record bleeding and spotting episodes daily using electronic diaries with preprogrammed questions.⁷ Bleeding was defined as vaginal blood loss requiring sanitary protection. Spotting was defined as vaginal blood loss that did not require sanitary protection. Women could only enter information for a given day between 12:00AM and 11:59PM. The electronic diary included an alarm set to the scheduled pill time and served as a reminder to complete the diary.⁷

RESULTS

Two randomized controlled trials and one post hoc analysis were used to determine if the combined oral contraceptive treatment of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol is effective in preventing unscheduled uterine bleeding. In each of the randomized controlled trials, the continuous data was able to be converted to dichotomous data. However, in the post hoc analysis study, the continuous data was not able to be converted.

The randomized controlled trial conducted by Guiahi et al. included 32 women of similar demographic and reproductive characteristics, all of which reported having bleeding that was extremely or very annoying.² See Table 1 for the study's inclusion and exclusion criteria. The

women were divided equally into groups either receiving 14 days of the oral contraceptive or an identically appearing placebo. Throughout the study, each participant completed a daily bleeding and pill taking diary to ensure compliance to the study. Only one participant in the oral contraceptive arm was noncompliant with protocol by missing a pill on days 11 and 12 and taking two pills on days 13 and 14.² Intent to treat analysis was performed and there was no loss to follow-up in the study. No adverse events were reported by any of the participants during the study. The primary outcome measured on completion of the study was temporary interruption of bleeding during therapy. Out of the participants in the experimental group receiving 14 days of a combined oral contraceptive containing 150 mcg levonorgestrel and 30 mcg ethinyl estradiol, 14 out of 16 participants (87.5%) admitted to interruption of bleeding compared to 6 out of 16 participants (37.5%) receiving an identical placebo.² The study determined that participants receiving the oral contraceptive were 11.7 times more likely than the placebo group to have temporary interruption of bleeding.² The study was determined to be statistically significant with a p-value <0.01 and a confidence interval (CI) of 95%. The results calculated from this randomized controlled trial are summarized in Table 2.

Table 2- Efficacy of the COC in preventing unscheduled uterine bleeding, Guiahi et al.²

CER	EER	RRR	ARR	NNT
0.375	0.875	1.33	0.5	2.0
Confidence Interval (CI)= 95%		p-value= <0.01		

Hou et al. conducted a double-blind, placebo-controlled, randomized controlled trial on 26 women reporting troublesome bleeding.⁶ The women were divided into an experimental group receiving a combined oral contraceptive of 150 mcg levonorgestrel and 30 mcg ethinyl

estradiol or an identical placebo for twenty-eight days. See Table 1 for the study's inclusion and exclusion criteria. On days 22-28 of the study, the participants were asked to attend a follow up visit to inform the study staff if the treatment had improved bleeding using a 5-point Likert scale. In both the experimental and control groups, 12 out of 13 women returned for follow up. In the group receiving the combined oral contraceptive, 11 (92%) noted significant improvement in bleeding compared to 5 (42%) receiving the placebo.⁶ The study was determined to be statistically significant with a p-value of 0.03. Losses to follow-up for the study was determined to be <20% since 24 out of 26 participants completed the study. The results calculated from this randomized controlled trial are summarized in Table 3. Adverse events reported in the study included headache (n=10), nausea or vomiting (n=3), cramping (n=3), and breast tenderness (n=4).⁶

Table 3- Efficacy of the COC in preventing unscheduled uterine bleeding, Hou et al.⁶

CER	EER	RRR	ARR	NNT
0.42	0.92	1.19	0.5	2.0
p-value= 0.03				

The post hoc analysis of a multicenter, open-label, 1-year, Phase 3 study conducted by Nappi et al. evaluated scheduled and unscheduled bleeding and spotting with the thought that ovarian suppression may result in improved cycle control and reduced risk of unscheduled bleeding.⁷ The study was conducted over one year with all participants receiving the treatment of a 91-day extended regimen of the combined oral contraception 150 mcg levonorgestrel and 30 mcg ethinyl estradiol for 84 days, and ethinyl estradiol 10 mcg in place of the traditional 7-day hormone-free interval.⁷ The study observed 799 women who completed at least one 91-day cycle

of therapy and reported their bleeding and spotting episodes using daily electronic diaries.⁷ See Table 1 for the study's inclusion and exclusion criteria. Table 4 summarizes the percentage of women for each cycle completed that reported unscheduled bleeding lasting less than six days or greater than six days. There was a 53% increase in the likelihood of women reporting 0-6 days versus greater than 6 days of unscheduled bleeding during days 1-84 for each additional 91-day cycle. The results led to an odds ratio (OR) of 1.531 and a confidence interval (CI) of 95% shown in Table 5.⁷ It was reported that there were more than one in five women reporting no bleeding by the third and fourth cycles of the study. Examination of study discontinuation showed 10% (80/799) discontinued due to an adverse event with 4% (32/799) due to bleeding and spotting adverse effects. The safety of this extended regimen combined oral contraceptive treatment is supported in that there was no accumulation of hormones, no unexpected changes to the endometrium, no effect of cycle length on hemostatic biomarkers, and similar incidence rates of adverse events over four years of continuous use compared with the conventional 28-day cycle.

Table 4- Percent of women reporting unscheduled bleeding, Nappi et al.⁷

Days of bleeding	Cycle 1 n=758	Cycle 2 n=625	Cycle 3 n=533	Cycle 4 n=446
0-6 Days	65%	81%	85%	85%
>6 Days	35%	19%	15%	15%

*n= number of participants for each cycle

Table 5- Efficacy of the COC in preventing unscheduled uterine bleeding, Nappi et al.⁷

Odds Ratio (OR)	Confidence Interval (CI)
1.531	95%

DISCUSSION

The two randomized controlled trials and post hoc analysis discussed in this systematic review determined the efficacy of a combined oral contraceptive's ability to treat bothersome unscheduled uterine bleeding. All three studies showed significant improvement of unscheduled bleeding with either minimal or no adverse events. Each study demonstrated statistically significant outcomes with p-values of <0.01, 0.03, or confidence intervals of 95%.^{2,6,7}

It is important to note that the studies done by Guiahi et al. and Hou et al. included participants that along with receiving the combined oral contraceptive during the study, also had an etonogestrel contraceptive implant with which they were experiencing bothersome uterine bleeding.^{2,6} Participants in the study conducted by Nappi et al. did not have an etonogestrel implant during the study.⁷

The combined oral contraceptive levonorgestrel and ethinyl estradiol is primarily used for the prevention of pregnancy.⁸ Some off-label uses include abnormal uterine bleeding, dysmenorrhea, hirsutism, menorrhagia, pain associated with endometriosis, and polycystic ovary syndrome (PCOS).⁸ Contraindications to usage include breast cancer or other estrogen or progestin dependent neoplasms, hepatic tumor or disease, pregnancy, and Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.⁸ It is also contraindicated in women at high risk of arterial or venous thrombotic diseases. The US boxed warnings for levonorgestrel and ethinyl estradiol include cigarette smoke and cardiovascular events.⁸

There were several limitations to the studies used in this review. The study conducted by Guiahi et al. had a limited protocol in which the first day of bleeding after therapy was the end of that individual's participation in the study.² This prevented the study from reporting on the long-

term bleeding patterns after a single 14-day treatment. A larger study would be needed to confirm the results of the sample and to determine if any patient characteristics influence success. Due to the small sample size in the study by Hou et al., the study population was too small for substantial subgroup and regression analyses.⁶ Since the study only included women seeking treatment for their bleeding, it did not represent all women who have a bleeding issue with the etonogestrel implant, but instead those who have more extreme bleeding complaints creating another limitation to this study. Limitations to the study by Nappi et al. include its open-label design and lack of a comparison group for evaluation of change in bleeding over time.⁷ The study also lacked correction to unscheduled bleeding/spotting when missed pill episodes were reported.

CONCLUSIONS

Based on the current research available, it can be determined that yes, the combined oral contraceptive of 150 mcg levonorgestrel and 30 mcg ethinyl estradiol is effective in treating bothersome, unscheduled uterine bleeding. All three studies in this review demonstrated statistically significant data that supported improvement in bleeding for participants receiving the combined oral contraceptive treatment.^{2,6,7} A flaw in the methods used by these studies that could be corrected in future studies is finding a less subjective way to monitor the amount of bleeding experienced by the participants. For example, bleeding that is considered heavy to one participant may be normal to another. Future study is warranted to further evaluate the long-term acceptability of bleeding, and length of the treatment's effect, after use of combined oral contraceptives to treat bothersome bleeding episodes.

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