ORIGINAL ARTICLE: CONTRACEPTION

Evaluation of an ultra-low-dose oral contraceptive for dysmenorrhea: a placebo-controlled, double-blind, randomized trial

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Objective: To evaluate the efficacy and safety of an ultra-low-dose oral contraceptive (NPC-01; 0.02 mg ethinyl estradiol and 1 mg norethisterone) in subjects with dysmenorrhea.
Design: Placebo-controlled, double-blind, randomized trial.
Setting: Clinical trial sites.
Patient(s): Two hundred fifteen subjects with dysmenorrhea.
Intervention(s): Subjects were randomly assigned to receive NPC-01, placebo, or IKH-01 (0.035 mg ethinyl estradiol and 1 mg norethisterone) for four cycles.
Main Outcome Measure(s): Total dysmenorrhea score (verbal rating scale) assessing pain on the basis of limited ability to work and need for analgesics.
Result(s): The reductions of total dysmenorrhea score and visual analog scale score after the treatment were significantly higher in the NPC-01 group than in the placebo group. Furthermore, the efficacy of NPC-01 was comparable to that of IKH-01. The overall incidence of side effects was significantly higher in the NPC-01 group than in the placebo group. All side effects that occurred in the NPC-01 group were previously reported in patients receiving IKH-01. No serious side effects occurred.
Conclusion(s): The ultra-low-dose contraceptive NPC-01 relieved dysmenorrhea as effectively as IKH-01. Thus, NPC-01 could represent a new option for long-term treatment of dysmenorrhea.
Clinical Trial Identification Number: NCT01129102. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Ultra-low-dose oral contraceptives, dysmenorrhea, placebo-controlled randomized trial

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Dysmenorrhea is the term used for describing painful menstrual cramps. It is a common gynecologic problem that can affect as many as 50% of women. Approximately 15% of these women suffer from pain severe enough to temporarily render them incapacitated, which results in absences from work or school (1). We previously conducted a randomized, controlled trial (RCT) with a placebo comparator that showed the efficacy of an oral contraceptive (OC), IKH-01 (0.035 mg ethinyl estradiol [EE] and 1 mg norethisterone [NET]), for dysmenorrhea associated with endometriosis and for primary dysmenorrhea (2, 3).

Ethinyl estradiol, which is contained in OC pills, reduces irregular uterine bleeding, a side effect of administration of progestin (4). However, EE increases the risk of venous thromboembolism (VTE), a serious although relatively rare disease. In a large-scale national cohort study on the association between OC pills and the risk of VTE in Denmark from 1995 to 2005, Lidegaard et al. (5) found that the risk of VTE depends on doses of the estrogen and types of progestin. These results were corroborated by the study of van Hylckama Vlieg et al. (6), who examined the association between OC pills and the risk of VTE in The Netherlands.

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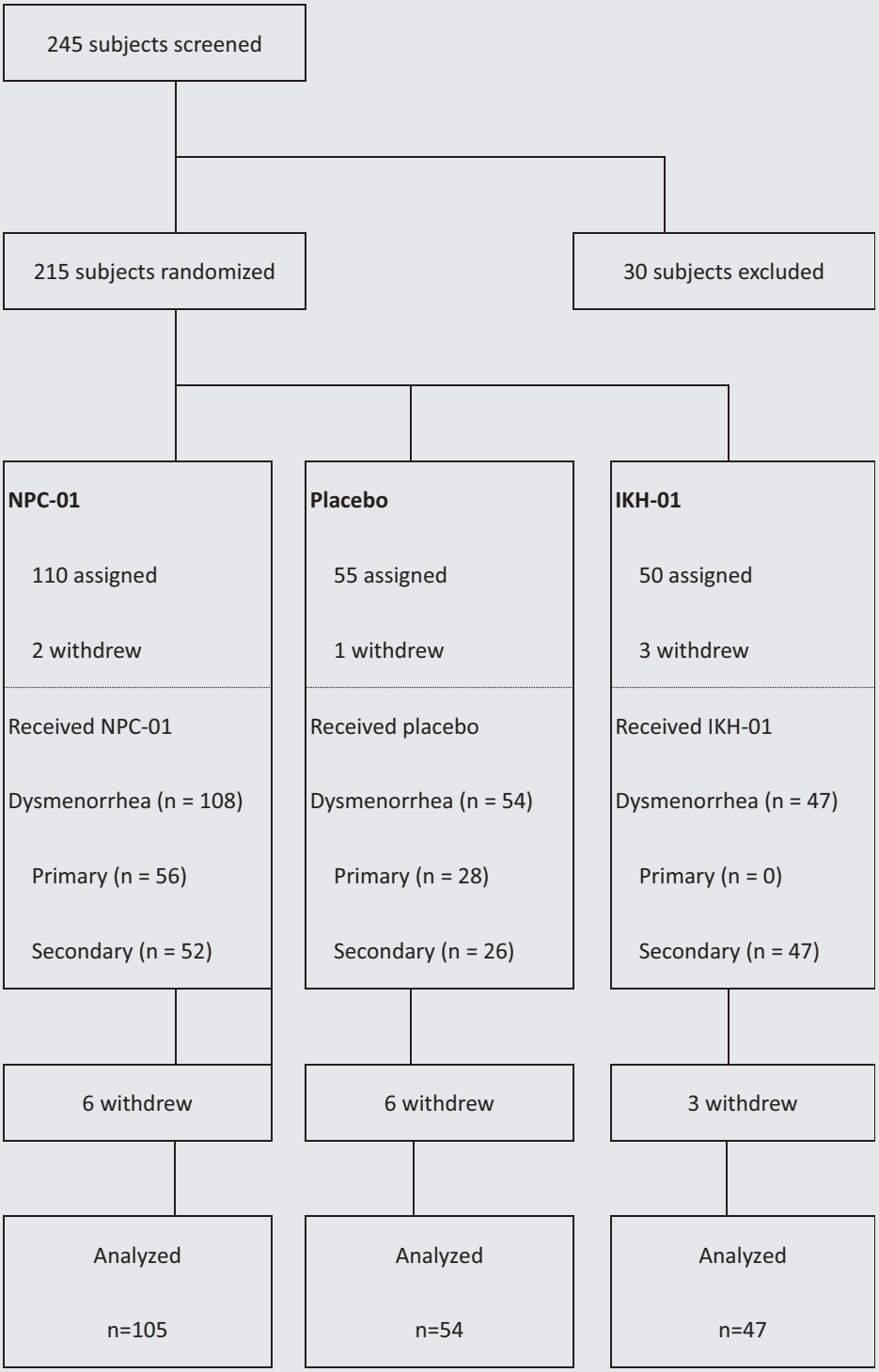
FIGURE 1



Flow diagram of the randomized, controlled trial.

Harada. Ultra-low-dose oral contraceptive for dysmenorrhea. Fertil Steril 2016.

Dysmenorrhea is categorized into two types, primary and secondary. Primary dysmenorrhea refers to menstrual pain without underlying pathology. The most common cause of secondary dysmenorrhea is endometriosis, ectopic growth of endometrial-like tissues outside the uterus, which affects 10% of women of reproductive age (7). The main clinical symptoms are dysmenorrhea, chronic pelvic pain, and infertility. Treatment of endometriosis may be surgical,