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Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices

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Abstract

Objectives: The objective was to measure the rate of unintended pregnancies in women using levonorgestrel-releasing intrauterine systems (LNG IUSs, releasing 20 mcg LNG daily) and copper intrauterine devices (IUDs) in a typical population of IUD users and to describe associated complications.

Methods: A multinational, prospective, non-interventional cohort study of new users of LNG IUS and copper IUDs was performed. Following a baseline survey, study participants and their physicians completed one follow-up questionnaire after 12 months. A multifaceted four-level follow-up procedure minimized loss to follow-up. Patient-reported outcomes were validated by the treating physicians.

Results: A total of 61,448 women with a newly inserted IUD were enrolled in six European countries between 2006 and 2012. The copper IUD cohort contained more than 30 different types. Validated 1-year follow-up information for 58,324 users between 18 and 50 years of age (70% using LNG IUS, 30% using copper IUDs) was collected. A total of 118 contraceptive failures occurred (26 LNG, 92 copper). Both types of IUD were highly effective, with overall Pearl indices of 0.06 [95% confidence interval (CI): 0.04–0.09] and 0.52 (95% CI: 0.42–0.64) for LNG IUS and copper IUDs, respectively. The adjusted hazard ratio for LNG IUS vs. copper IUDs was 0.16 (95% CI: 0.10–0.25). Tenty-one pregnancies (7 LNG IUS, 14 copper IUD) were ectopic, yielding an adjusted hazard ratio for ectopic pregnancy of 0.26 (95% CI: 0.10–0.66).

Conclusions: The contraceptive failure rate was low with both IUDs. However, the LNG IUS was associated with a significantly lower risk of pregnancy, including ectopic pregnancy, than the copper IUDs.

Implications: To our knowledge, this is the first large-scale, multinational, prospective epidemiological study to measure and compare the contraceptive effectiveness of LNG IUSs and copper IUDs during routine clinical practice. Clinicians and patients should be aware of differences in rates of unintended pregnancies and associated complications in relation to IUD us.

Keywords: Intrauterine device (IUD); Levonorgestrel (LNG); Copper; Ectopic pregnancy; EURAS IUD

1. Introduction

Contraceptive failure rates for both copper intrauterine devices (IUDs) and levonorgestrel-releasing intrauterine systems (LNG IUSs) are among the lowest for reversible methods of contraception [1,2], with studies of various types showing rates of around 0.1–2.2 per 100 WY for copper IUDs and 0.1–0.6 per 100 WY for LNG IUSs [3–10]. The respective ectopic pregnancy rates range from 0.02–0.2 in LNG IUS users and from 0.1–0.8 in copper IUD users [3,4,8,11].

Results from large-scale prospective studies on contraceptive effectiveness and pregnancy-related outcomes, including ectopic pregnancies, have not previously been available for LNG IUS or for LNG IUS in comparison to copper IUDs. This article presents the final results on pregnancy-related outcomes from the European Active Surveillance Study for Intrauterine Devices (EURAS IUD). Results on uterine perforation from the EURAS IUD study are reported separately [12].

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The objective of this article was to compare the contraceptive effectiveness and pregnancy-related outcomes, including ectopic pregnancies, for users of LNG and copper IUDs.

2. Methods

The purpose of the EURAS IUD was to identify and compare the risks of LNG IUS and copper IUD use in a population of typical users of IUDs. The methods are described in detail elsewhere [12]. The primary outcome of interest in EURAS IUD was the incidence of uterine perforation. A further a priori objective of the EURAS IUD study (and the focus of this article) was to compare the contraceptive effectiveness and pregnancy-related outcomes for users of LNG versus copper IUDs, including ectopic pregnancies.

EURAS IUD was a multinational, prospective, controlled, long-term cohort study with recruitment in six European countries (Austria, Finland, Germany, Poland, Sweden, UK) from 2006 to 2012. Its two cohorts consisted of new users of LNG and copper IUDs.

A non-interference approach was chosen; participating health care providers prescribed and provided the method as they normally would. The EURAS IUD study was approved by the ethical committee of the physicians' association in Berlin, Germany, and the Ethics Committee of Hospital District of Southwest Finland. The other participating countries accepted these approvals. The final results of this study were reported to the European Medicines Agency, to the US Food and Drug Administration and other health authorities.

Recruitment of study participants was conducted via a network of health care professionals (HCPs), such as gynecologists and midwives who regularly insert IUDs, either office based or in specialized clinics. All women with a newly inserted IUD were eligible for enrollment. Therefore, the copper IUD cohort consists of numerous different types of copper IUDs primarily characterized here by their surface area (<300 mm^2, ≥ 300 mm^2). After the decision to initiate an IUD was made, participating HCPs asked the women whether they were willing to participate in the study. Because of the non-interference approach, eligibility criteria were minimal: these included a willingness to sign an informed consent form and data privacy form, and an absence of a language barrier that could prevent the patient from completing the questionnaires.

At the time of IUD insertion, study participants completed a baseline questionnaire on which they recorded information about their state of health and potential risk factors. These included medical and lifetime reproductive history, medication history, history of contraceptive use, age, body mass index (BMI), smoking, alcohol, exercise and lifting of heavy objects, and level of education. Study participants and the inserting HCP received a follow-up questionnaire 12 months after enrollment. The follow-up survey recorded information about any potential complications associated with the IUD, medical checkups, illnesses, hospitalization and pregnancy that occurred during the time period since IUD insertion.

All events and pregnancy-related outcomes reported by study participants, including subjectively perceived symptoms and the diagnoses as understood by them, were entered into the study database. These report forms were immediately passed on to the study center's medical reviewer or review group, which contacted the participants for clarification if necessary and the treating physicians for validation. The follow-up questionnaire sent to physicians 12 months after insertion recorded any pregnancy outcomes in addition to examination dates, IUD position (including unnoticed expulsion), uterine perforation, complications and patients' medical conditions.

The sample size of this study was chosen to test noninferiority of LNG IUS regarding the perforation risk (the primary outcome of interest in this study) in comparison to copper IUDs. Sample size calculations showed that 60,000 participants would be sufficient to exclude a 1.7-fold risk. These calculations were based on an estimated perforation rate of 0.5 per 1000 insertions, a one-sided α of 0.025 and a power $(1-\beta)$ of 0.80.

Crude as well as adjusted hazard ratios (HRs) were calculated. The appropriate confounding variables were built into the model. Based on the expectation of a small absolute number of unintended pregnancies, the confounding variables were limited to a small number of predefined risk factors (age, BMI, parity) recommended by the independent Safety Monitoring and Advisory Council. All analyses were performed with the statistical package STATA 9.0.

3. Results

Recruitment started in Germany, Austria and Finland in 2006, the United Kingdom in 2008, Sweden in early 2009 and Poland in November 2009. Recruitment stopped at the end of 2012. In total, 61,448 women with a newly inserted IUD were enrolled by more than 1200 participating HCPs. In total, 1235 women, or 2.0% (1.7% for LNG IUS, 2.8% for copper IUD), were lost to follow-up during the 1-year follow-up period. For all analyses regarding unplanned pregnancies, only women in the age group of 18–50 years were included. This analysis includes validated follow-up information for a total of 58,324 women in this age group: 41,001 users of LNG IUS and 17,323 users of copper IUDs, resulting in 44,633 and 17,703 WYs of observation, respectively. More than 30 types of copper IUDs were included in the copper IUD cohort, the most frequent ones being NovaT (200 or 380) with 37%, T Safe Cu 380 with 18% and Multiload CU (250 or 375) with 14%. The copper surface areas were less than 300 mm^2, 300 mm^2 and more than 300 mm^2 in 7.8%, 1.6% and 71.3% of the inserted copper IUDs inserted in this study, respectively. In 19.3%, the surface area was not known.