

Original research article

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

Klaas Heinemann*, Suzanne Reed, Sabine Moehner, Thai Do Minh

ZEG-Berlin, Chausseestrasse 115, 10115 Berlin, Germany

Received 2 October 2014; revised 8 January 2015; accepted 12 January 2015

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). Twenty-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 use.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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].

* Corresponding author at: ZEG-Berlin Center for Epidemiology and Health Research Invalidenstrasse 115 10115 Berlin Germany. Tel.: +49 30 945 101 24, +49 1717 554 556 (mobile); fax: +49 30 945 101 26.
E-mail address: k.heinemann@zeg-berlin.de (K. Heinemann).

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 ($<300 \text{ mm}^2$, $\geq 300 \text{ mm}^2$). 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.

The women in the LNG IUS and copper IUD cohorts had mean ages of 37.4 and 33.3 years, respectively. More than 40% of the LNG IUS users in this study were over 40 years of age, as compared to only 24% in the copper IUD group. Another difference between cohorts with potential impact on contraceptive failure included the prevalence of breastfeeding at time of insertion (9.2% vs. 14.6%). In the LNG IUS cohort, 19.8% of users had given birth during the 12 months preceding insertion, compared to 28.7% of copper IUD users. Some 93.0% of the LNG IUS users and 88.0% of the copper IUD users had ever been pregnant. The proportion of smokers in both cohorts was comparable. The educational level of the copper IUD users and LNG IUS users was comparable: 55.6% of the copper IUD users had at least university entrance level, compared to 49.6% of the LNG IUS users. More detailed information about baseline characteristics has been reported separately [12].

One hundred eighteen validated, unintended pregnancies occurred during the 1-year follow-up period: 26 in LNG IUS users and 92 in copper IUD users. Twenty-nine of these unintended pregnancies (13 LNG IUS, 16 copper IUD) occurred after an unrecognized IUD expulsion and were therefore considered to have resulted from a failure of the contraceptive method. They were therefore included in this analysis.

In 27 pregnant women (1 LNG IUS, 26 copper IUD), the IUD was found dislocated (not in the uterine cavity, but still in the body). While it is possible to attribute dislocation of the IUD to the mechanical forces of the pregnancy itself, over 80% of these cases were diagnosed in the very early stages of pregnancy (6 weeks or less after conception), most likely before the position of the IUD could have been affected.

In three cases of unintended pregnancy (three copper IUD) the IUD was perforated. The remaining unintended pregnancies occurred with the IUD entirely within the uterus.

Contraceptive failure rates differed markedly between cohorts. The overall Pearl index (PI; pregnancies per 100 WYs) in the LNG IUS cohort was 0.06 [95% confidence interval (CI): 0.04–0.09]; the respective PI for the copper IUD users was 0.52 (95% CI: 0.42–0.64). The life-table estimates of the rate of contraceptive failure for the first year of use were 0.07% and 0.63% for LNG IUS and copper IUD, respectively.

This resulted in a crude risk ratio for LNG IUS use compared to copper IUD use of 0.11 (95% CI: 0.07–0.17). To control for potential differences in contraceptive failure rates associated with different surface areas in the copper IUD cohort, stratified analyses were conducted using 300 mm² as the cutoff point (<300 mm², ≥300 mm²). The pearl indices for copper IUD with less than 300 mm² was 0.56 (95% CI: 0.24–1.09), and 0.62 (95% CI: 0.50–0.78) for 300 mm² or greater.

Age distribution differed markedly between cohorts, so the life-table estimates of the rate of contraceptive failure for the first year of use for the cohorts were therefore calculated

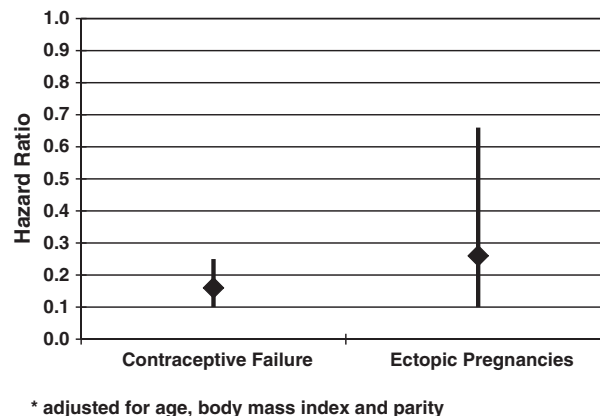


Fig. 1. Relative risk of contraceptive failure and of ectopic pregnancy in LNG IUS compared to copper IUD users: Adjusted* HR (95% CI).

stratified by age groups (18–<30 years, 30–<40 years, 40–50 years) (Table 1). The respective estimate for LNG IUS and copper users in the age group of 18–35 years was 0.15 and 0.97, respectively. The risk of contraceptive failure in LNG IUS users compared to copper IUD users was statistically significantly lower in all age groups except for women between 40 and 50 years of age.

Stratification by country also showed statistically significantly lower risks for LNG IUS users compared to copper IUD users in all countries except for Poland, where the sample size was too small. In Poland, no pregnancies with LNG IUS occurred, and there were four pregnancies with copper IUDs (data not shown).

Cox regression analysis that included the predefined prognostic factors age, BMI, and parity yielded an adjusted HR of 0.16 (95% CI: 0.10–0.25) for LNG vs. copper IUDs (Fig. 1). The same comparison excluding those pregnancy cases with an unnoticed expulsion of the IUD yielded an adjusted HR of 0.10 (95% CI: 0.05–0.18).

Significant differences between cohorts were evident in the ectopic pregnancy rates. Seven women with LNG IUS and 14 women with copper IUDs had an ectopic pregnancy, resulting in incidence rates of 0.02 per 100 WY (95% CI: 0.01–0.03) and 0.08 per 100 WY (95% CI: 0.04–0.13), respectively. The proportion of ectopic pregnancies among all contraceptive failure pregnancies was higher in LNG IUS users compared to copper IUD users (27% vs. 15%, $p = .16$), but due to the substantially lower risk of contraceptive failure in LNG IUS users, the overall risk for ectopic pregnancies was significantly lower in LNG IUS users compared to copper IUD users [HR 0.20 (95% CI: 0.08–0.48)]. The HR did not change substantially after adjustment for age, BMI and parity [HR 0.26 (95% CI: 0.10–0.66)] (Fig. 1).

Two of the seven ectopic pregnancies in LNG IUS users and 10 of the 14 ectopic pregnancies in copper IUD users resulted in a salpingectomy. In addition, two of the extrauterine pregnancies in copper IUD users led to removal of an ovary.

Table 1
Life-table estimates for contraceptive failure in first year of use by IUD cohort by age group

Age group	LNG IUD		Copper IUD	
	No. of pregnancies	LT est. (95% CI)	No. of pregnancies	LT est. (95% CI)
18–<30 years	7	0.16 (0.03–0.28)	54	1.35 (0.95–1.76)
>= 30–<40 years	16	0.12 (0.06–0.18)	36	0.57 (0.37–0.77)
>= 40–<51 years	3	0.01 (0–0.03)	2	0.05 (0–0.12)

4. Discussion

The contraceptive effectiveness was very high in both cohorts in this study. However, use of LNG IUS in this study was associated with one eighth the incidence of pregnancy during the first year of use, including a marked reduction in ectopic pregnancy, compared to use of a copper IUD. A discrepancy this large is unlikely to be explained by effects of selection bias or information bias [13–16]. Differential losses to follow-up are also unlikely to have caused the disparity: the study achieved a low overall loss to follow-up with 1.7% and 2.8% in the LNG IUS and copper IUD users, respectively. Our analysis controlled for important potential confounding factors, and the results were unchanged. The significantly lower risk for ectopic pregnancy in LNG IUS users compared to copper IUD users is not likely to be due to chance. Hence, we believe these findings are robust.

A wide range of pearl indices for LNG IUS has been reported in the scientific literature. A cross-sectional study by Backman in more than 17,000 women, for example, showed a PI of 0.11 [4]. Similar results of 0.1–0.2 were found in reviews of randomized clinical trials [7–9]. Other authors have found higher rates of contraceptive failure. Cox, for example, found a PI of 0.6 in an open-label, single-group study in almost 600 women [6].

As in our study, PIs for various copper IUD systems are generally found to be higher than those for LNG IUS, although not necessarily to the extent that we found here. A Cochrane review of randomized controlled trials reported PIs of 0.5–2.2 for copper IUDs with a surface area of less than 300 mm², and of 0.1–1.0 for greater than 300 mm² [5]. Sivin et al. and Mansour et al. reviewed several randomized clinical trials and found results in the same range [8,10]. Two additional randomized clinical trials in more than 2000 women, respectively, showed similar PIs of 0.3–1.3 [3,7].

These results on ectopic pregnancies are consistent with findings from other studies. Previously reported ectopic pregnancy rates for LNG IUS users ranged from 0.02 to 0.2 per 100 WY, and rates for copper IUD users were from 0.1 to 0.8 per 100 WY [3,4,8,11].

In this study, we collected no information on concurrent use of other contraceptive methods. However, use of additional contraceptive methods is probably more prevalent in younger women not yet living in stable partnerships. As the copper IUD cohort was markedly younger, this would probably have led to an underestimation of the risk ratio rather than an overestimation.

This epidemiological study investigated routine clinical practice in an international environment and probably allows extrapolation to other populations. The greater effectiveness of the LNG IUS was evident for all age groups of women and is unlikely to be due to bias, confounding or chance. Clinicians and women seeking contraception need to be aware of these differences in the contraceptive effectiveness in contemporary IUDs.

References

- Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. *N Engl J Med* 2012;366(21):1998–2007.
- Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83(5):397–404.
- Andersson K, Odland V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994;49(1):56–72.
- Backman T, Rauramo I, Huhtala S, Koskenvuo M. Pregnancy during the use of levonorgestrel intrauterine system. *Am J Obstet Gynecol* 2004;190(1):50–4.
- Kulier R, O'Brien PA, Helmerhorst FM, Usher-Patel M, D'Arcangues C. Copper containing, framed intra-uterine devices for contraception. *Cochrane Database Syst Rev* 2007;4:1-152 [CD005347].
- Cox M, Blacksell S. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 12-month report. *Br J Fam Plann* 2000;26(3):143–7.
- Sivin I, el Mahgoub S, McCarthy T, Mishell Jr DR, Shoupe D, Alvarez F, et al. Long-term contraception with the levonorgestrel 20 mcg/day (LNG 20) and the copper T 380Ag intrauterine devices: a five-year randomized study. *Contraception* 1990;42(4):361–78.
- Sivin I. Dose- and age-dependent ectopic pregnancy risks with intrauterine contraception. *Obstet Gynecol* 1991;78(2):291–8.
- Stoddard A, McNicholas C, Peipert JF. Efficacy and safety of long-acting reversible contraception. *Drugs* 2011;71(8):969–80.
- Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. *Eur J Contracept Reprod Health Care* 2010;15(1):4–6.
- Ganacharya S, Bhattoa HP, Batár I. Ectopic pregnancy among non-medicated and copper-containing intrauterine device users: a 10-year follow-up. *Eur J Obstet Gynecol Reprod Biol* 2003;111(1):78–82.
- Heinemann K, Reed SR, Moehner S, Thai DM. Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception* 2015;91(4):274–9.
- Taubes G. Epidemiology faces its limits. *Science* 1995;269(5221):164–9.
- Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
- Grimes DA, Schulz KF. False alarms and pseudo-epidemics: the limitations of observational epidemiology. *Obstet Gynecol* 2012;120(4):920–7.
- Khouri MJ, James LM, Flanders WD, Erickson JD. Interpretation of recurring weak associations obtained from epidemiologic studies of suspected human teratogens. *Teratology* 1992;46(1):69–77.