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Original research article

Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices

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Abstract

Objectives: The objectives were to identify and compare the incidence of uterine perforation and other medically adverse events associated with levonorgestrel-releasing intrauterine systems (LNG-IUSs, releasing 20 mcg LNG daily) and copper intrauterine devices (IUDs) under routine conditions of use in a study population representative of typical users.

Methods and materials: This is a multinational, prospective, non-interventional cohort study with new users of LNG-IUSs and copper IUDs. In addition to a baseline questionnaire, women and their treating health care professional completed a single follow-up questionnaire after 12 months. All patient-reported outcomes were validated by the treating physicians.

Results: A total of 61,448 women in six European countries were followed between 2006 and 2013 for more than 68,000 women-years of observation (70% LNG, 30% copper devices). Overall, 81 uterine perforations were reported: 61 for LNG-IUSs [1.4 per 1000 insertions (95% confidence interval {CI}: 1.1–1.8)] and 20 for copper IUDs [1.1 per 1000 insertions (95% CI: 0.7–1.7)], for an adjusted risk ratio (RR_{adj}) of 1.6 (95% CI: 1.0–2.7) when adjusted for age, body mass index, breastfeeding at time of insertion and parity. Breastfeeding at time of insertion was associated with a sixfold increase (RR 6.1, 95% CI: 3.9–9.6), with no differences between LNG and copper IUD users. Sixty-three of the total 81 perforations were associated with previously suspected risk factors (e.g., breastfeeding, time since last delivery ≤36 weeks). No perforations led to serious illness or to injury of intra-abdominal or pelvic structures.

Conclusions: Uterine perforation incidence in this study was low, with a benign clinical course thereafter. The LNG-IUSs and copper IUDs did not have clinically important differences in perforation rates.

Implications: The European Active Surveillance Study on Intrauterine Devices is the first large-scale, prospective, noninterventional study to compare the perforation risk in LNG-IUS and copper IUD users. It is the first to examine the independent roles that breastfeeding status and postpartum status have on perforation risk. Conducted during routine clinical practice, the findings are generalizable to broader populations.

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Keywords: Intrauterine device; Levonorgestrel; Copper; Uterine perforation

1. Introduction

Uterine perforation is a potentially serious complication of intrauterine device (IUD) use. Reported incidences range from 0.3 to 2.6 per 1000 insertions for levonorgestrel-releasing intrauterine systems (LNG-IUSs) (releasing 20 mcg LNG daily) and 0.3 to 2.2 for copper IUDs [1–6]. Extensive clinical experience with LNG-IUSs suggests that serious outcomes such as peritonitis caused by perforation of the uterine wall after insertion are rare; however, results from large prospective studies with defined diagnostic follow-up procedures are not available. Scientific evidence for the safety of other IUDs — almost exclusively copper IUDs — is also unsatisfactory and not necessarily generalizable to a population of LNG-releasing IUD users.

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Several risk factors for uterine perforation have been described. Breastfeeding [5,7] and postpartum state [1,8] have been associated with an increased perforation risk, but these risk factors have previously not been examined independently of each other. Other risk factors include lack of experience of the healthcare professional (HCP) performing the insertion [6,8,9], multiparity [7], nulliparity [1,9] and history of cesarean delivery [1]. These findings, however, are not consistent across studies. The European Active Surveillance Study on Intrauterine Devices (EURAS IUD) aimed to compare the uterine perforation risk in users of LNG- and copper IUDs in routine clinical practice.

2. Methods

2.1. Study design

EURAS IUD was a prospective cohort study with recruitment in six European countries from 2006 to 2012. Its two cohorts consisted of new users of levonorgestrel-releasing IUDs (releasing 20 mcg LNG daily) and all copper IUDs currently used in the participating countries. A non-interference approach was chosen to avoid influencing the health care professionals' prescribing behavior and to provide standardized, comprehensive and reliable information on these IUDs under routine medical conditions. The study was approved by the ethical committee of the physicians' association in Berlin, Germany, and the Ethics Committee of Hospital District of Southwest Finland.

2.2. Study objectives

The primary outcome of interest was the incidence of uterine perforation. This included an estimate of the perforation incidence associated with IUD insertion, the proportion of uterine perforations associated with serious clinical complications, the interval between IUD insertion and diagnosis of uterine perforation and the impact of postpartum IUD insertion on the uterine perforation rate. For each of these outcome measures, comparisons were made between LNG and copper IUDs. For the analysis, the most conservative approach was used to define perforation. All events reported by the participating HCPs and/or patients where any part of the device was considered to have crossed the endometrium and entered the myometrium were considered a perforation.

The secondary objective of this study was to compare the contraceptive effectiveness and pregnancy-related outcomes (including ectopic pregnancies) for users of LNG and copper IUDs, and also the incidence of other medically relevant adverse events. This report focuses on only the primary objective; the secondary outcome will be described in another report.

2.3. Study population

Study participants were recruited via a network of 1200 HCPs (e.g., gynecologists, midwifes, specialized clinics) who regularly insert IUDs. All women with a newly inserted IUD were eligible for enrollment. Study participants consisted of first-ever IUD users and consecutive users (previous IUD use). After a patient decided to use an IUD, participating HCPs invited the patient 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.

2.4. Baseline and follow-up questionnaires

At the time of IUD insertion, study participants completed a baseline questionnaire designed to collect information relating to their medical and gynecological history (including medication and contraceptive use), age, body mass index (BMI), lifestyle factors (smoking, alcohol consumption, exercise, heavy lifting) and level of education. Breastfeeding status and time since last delivery were of particular interest. On a separate form, the women provided their contact details (postal and email addresses and telephone numbers) and those of an additional contact, such as a relative or friend, and also those of their gynecologist or primary care physician. Contact data were documented separately in compliance with data protection regulations.

The follow-up questionnaire was sent to study participants 12 months after the IUD insertion. It contained questions about the insertion procedure, its aftermath, complications, medical checkups, illnesses, hospitalization and pregnancy, along with changes in physician contact information.

All patient-reported events of interest were validated by direct contact with the study participants and the diagnosing and/or treating physicians. Participating HCPs followed their participating patients in accordance with customary procedures for newly inserted IUDs. To capture information relating to the routinely conducted post-insertion examination during the first year, follow-up questionnaires were sent 1 year after insertion to the clinician. The clinician was asked to record information on checkup dates, IUD position, diagnosed perforations and patients' medical conditions for those patients who had returned to the respective clinician during the first year post-insertion. The clinician was not required to actively follow-up patients who did not come back for a postinsertion checkup.

In order to minimize loss to follow-up, a multifaceted, four-level follow-up process was used. The first level consists of mailing the follow-up questionnaire, as well as two reminder letters in case of no response. If these actions did not reinstate contact with the women, multiple level 2 attempts are made to contact the women by phone or, if necessary, their friends/relatives who were listed as additional contacts, in addition to the gynecologists/primary care physicians. Parallel level 3 activities consist of searches in national and international telephone and address directories. If they are not successful, an official address search via the respective governmental

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