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Uterine Perforation with the Levonorgestrel-Releasing Intrauterine Device

Analysis of Reports from Four National Pharmacovigilance Centres

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Abstract

Background: Levonorgestrel-releasing intrauterine devices (LNG-IUD) are commonly used for contraception and other indications in many countries. National pharmacovigilance centres have been receiving reports from healthcare professionals and patients of uterine perforation associated with the use of these LNG-IUDs.

Methods: National pharmacovigilance centres in the Netherlands, New Zealand, Switzerland and Germany did a search on their adverse drug reaction databases for reports of cases of uterine perforation after insertion of a LNG-IUD received between the introduction of the LNG-IUD onto the market in the late 1990s and 15 July 2007.

The number of women affected and patient characteristics such as age, parity and breastfeeding status were examined. In addition, the method of detection of the perforation and the time until discovery of the perforation were analysed.

Results: Between the introduction of the LNG-IUD onto the market in each country and 15 July 2007, 701 cases of uterine perforation with a LNG-IUD were reported; 8.5% of the perforations were detected at the time of insertion. Abdominal pain and control/check-up visits were the most common events that lead to the detection of a perforation. Of 462 women known to be parous, 192 (42%) were breastfeeding at the time the perforation was discovered.

Conclusions: Uterine perforations can be asymptomatic and may remain undetected for a long time after IUD insertion. Abdominal pain, control/check-up visits or changes in bleeding patterns are triggers for detection of perforation and should therefore be taken seriously.

Background

The levonorgestrel-releasing intrauterine device (LNG-IUD) Mirena® consists of a polyethylene T-shaped reservoir containing levonorgestrel. Over its effective lifespan of 5 years it releases, on average, levonorgestrel 20 μg/day. Since its introduction in the late 1990s, millions of women in more than 100 countries worldwide have used the LNG-IUD for contraception.[1,2] In addition, the LNG-IUD is used in some countries for its non-contraceptive beneficial effects on menorrhagia, dysmenorrhoea and endometriosis.[3,4] Recent concerns with Mirena® include safety of use in relation to breast cancer[5,6] and ectopic pregnancy.[7] Another complication that can occur after insertion of any IUD is uterine perforation.[8-11] Perforation of the uterus is a serious medical event that, even though it is sometimes asymptomatic, can cause severe morbidity.[12,13]

Recently, in Canada and Switzerland, a 'Dear Healthcare Professional Letter' was sent to inform health professionals regarding essential precautions in order to prevent uterine perforation with the use of LNG-IUDs.[14,15]

National pharmacovigilance centres have been receiving reports of uterine perforation after insertion of LNG-IUDs. We analysed the pooled data from pharmacovigilance centres in the Netherlands, New Zealand, Switzerland and Germany. The aim of this study is to provide a descriptive analysis of the reports as received by these four countries.

Methods

Data Collection

We searched the databases of the national pharmacovigilance centres in the Netherlands, New Zealand, Switzerland and Germany for all reports coded as 'uterine perforation' associated with use of the LNG-IUD since the start of marketing in each country until 15 July 2007.

The Netherlands Pharmacovigilance Centre, Lareb collects cases from spontaneous reporting by health professionals and consumers, either directly or via the Marketing Authorization Holder.

Cases from Switzerland originate from spontaneous reporting by health professionals. Reports were collected by Swissmedic, the national Swiss Pharmacovigilance Centre, through its six regional pharmacovigilance centres.

Cases from New Zealand were collected by the Intensive Medicines Monitoring Programme (IMMP), a prescription-event monitoring programme that also receives spontaneous reports for monitored medicines/devices.[16]

The German cases were collected by the Federal Institute for Drugs and Medical Devices (BfArM), which receives reports directly from health professionals or via the Marketing Authorization Holder.

Our study is a retrospective inventory of the information provided in these reports. Data analysis was done in SPSS version 15 (SPSS Inc., Chicago, IL, USA) when appropriate.

Results

A total number of 701 cases of uterine perforation have been reported. Of these cases, 514 (73%) originated from Germany, 104 (15%) from the Netherlands, 67 (10%) from Switzerland and 16 (2%) from New Zealand. The age of the patients involved was reported in 579 (83%) cases. The mean age was 33.5 years, ranging between 15 and 53 years. Further details are given in table I.

Indication for Use

The indication for use of the LNG-IUD was provided in 124 of the 701 cases (18%). Indication for use was described as solely for contraception in 108/124 cases (87%), and in 4/124 cases (3%) the indication for use was menorrhagia or dysmenorrhoea. In four cases (3%), both contraception and an abnormal menstruation were mentioned as the indications for use.

Parity and Breastfeeding

Parity (nulliparous vs primiparous or multiparous) was reported in 485 of 701 cases (69.2%). Of these 485 cases, 23 women (4.7%) were nulliparous and 462 women (95.3%) were parous. The mean time between delivery and insertion was 3.64 months (ranging from 28 days to 5 years). Of the 462 parous women, 192 (41.6%) were breast-

Table I. General characteristics per country

Parameter	Germany	Netherlands	New Zealand	Switzerland
Pharmacovigilance system	Spontaneous reporting	Spontaneous reporting	Spontaneous reporting + IMMP	Spontaneous reporting
Start of marketing	1997	1999	1998	1995
No. of reports for Mirena®	1754	491	2316	417
No. of all reports of uterine perforation for Mirena®	514	104	16	67
Percentage perforations of all reported events	29.3	21.2	0.7	16.1

IMMP = Intensive Medicines Monitoring Programme.

feeding their babies at the time the perforation was discovered. In 49 (17.7%) of these 462 women reported to be parous, information about breastfeeding was not provided, but it was explicitly reported that the LNG-IUD was inserted postpartum.

Time to Detection of Perforation

The time between IUD insertion and detection of the uterine perforation was mentioned in 559 reports (80%). The mean time to detection was 306 days. In 47 of these cases (8.4%), the perforation was suspected or discovered at the time of insertion. In 143 cases (25.6%), the discovery took place after more than 1 year.

In 102 cases (18%), uterine perforation was diagnosed during a control/check-up visit, for instance when the threads of the IUD were not visible.

Clinical Presentation

In 285 reports (41%), information was provided about one or more initial complaints that lead to the discovery of the uterine perforation. This concerned an abnormal bleeding pattern in 77 of these 285 cases (27.0%). Abdominal pain was present in 217 of them (76.1%). In 51 cases (17.9%), unintended pregnancies lead to the discovery of the uterine perforation. It was reported that the diagnosis of uterine perforation was confirmed by ultrasound in 302 of all reported cases (43%), by MRI in 18 cases (3%), by CT in 47 cases (7%) and by x-ray in 260 cases (37%). In 58 cases (8%), a laparoscopy was needed to confirm the diagnosis.

Removal of the Intrauterine Device

Information about the removal of the IUD was available in 545 cases (78%). In these 545 cases, nine (1.7%) cases required hysteroscopy to remove the IUD, laparoscopy was used in 384 cases (70.5%) and laparotomy was needed in 29 cases (5.3%). In 109 cases (20.0%), it was reported that the IUD had been removed but the method applied was not specified. In 14 cases (2.6%), the IUD had not been removed at the time of reporting of the event. Information about the presence of the IUD at the time of reporting or method of removal was not available in 156 cases.

Qualification of the Health Professional Performing the Insertion

The qualification of the health professional performing the insertion differs between countries. In Germany and Switzerland, Mirena® is generally inserted by gynaecologists. In New Zealand, 34% are inserted by general practitioners and 66% by hospital doctors. In the cases reported in the Netherlands, 27.9% were inserted by general practitioners, 54.8% in a hospital setting by gynaecologists and 17.3% by other health professionals.

Discussion

A uterine perforation is a serious event that can lead to serious and life-threatening complications[12] or, when the contraceptive effect is reduced by dislocation, to pregnancy.

We have analysed 701 cases of uterine perforation associated with the LNG-IUD Mirena®

reported to four national pharmacovigilance centres since the start of marketing to 15 July 2007. Three of the four countries received these reports through spontaneous reporting systems, which rely on what health professionals and patients consider important to report. New Zealand has a prescription-event monitoring system (the IMMP), which has studied the LNG-IUD for several years.[9,14] This programme includes the collection of spontaneous reports for the monitored medicines. The intensive monitoring of the LNG-IUD in New Zealand may explain the higher total number of reports for this device compared with that from other countries, and may be a reason for the lower proportion of all reports coded as uterine perforation (see table I).

The vast majority of cases in this international case series result from spontaneous reporting, which is known to have the limitation of underreporting;[17,18] therefore, the actual number of perforations in the four countries is likely to be higher.

Incidence Rates for Uterine Perforation

Incidence figures cannot be estimated based on data presented in this report as the exposed population is not accurately known. In the published literature, uterine perforation with the LNG-IUD has been described,[8,10,19] but most of the available information on incidence rates, patient characteristics and risk factors for uterine perforation originates from copper IUDs.[9,20] Uterine perforations with non-hormonal IUDs ranges from 0.05 to 1.6[9] per 1000 insertions reported.[9,12,20] The incidence rate for uterine perforation with LNG-IUDs from a retrospective multicentre study in which gynaecologists were sent questionnaires was 2.6 per 1000 insertions.[21] None of these cases were reported to a pharmacovigilance centre before the study was performed.

In an observational cohort study of the LNG-IUD performed by the New Zealand IMMP, the perforation rate was 0.9 per 1000 insertions.[8] A randomized trial comparing the LNG-IUD and the copper IUD TCu380Ag reported incidence rates at 7 years of 0.1 and 0.0 per 100 years, respectively, for uterine perforation, and 0.1 and 0.0 per 100 years, respectively, for IUD embedded. Women using the LNG-IUD accrued 3416 years of experience, and those with the copper IUD accrued 3975 years of use.[22]

However, there are no data available that directly compare the perforation rates of copper IUDs and the LNG-IUD that include a sufficient number of insertions to be able to provide adequate statistical power to detect a difference in the frequency of perforations. In this respect, a prospective cohort study is ongoing, which is expected to provide final results in 2012. The interim results of this study have recently been presented as a poster.[23] The authors calculated incidence rates of 0.53 and 0.44 per 1000 insertions for the LNG-IUD and copper IUDs, respectively, based on 12 565 and 4651 patients with validated 1-year follow-up information.

In general, inexperienced inserters may account for higher perforation rates than experienced inserters. In an earlier study, the rate of difficult insertions was found to be inversely related to the number of devices inserted per doctor[8] and it has been recommended that professionals who have only occasional opportunities for IUD insertion should refer the woman to a physician who is more experienced in IUD insertion.[20]

Time to Detection of Uterine Perforation

The fact that only 8.4% of the reported perforations were discovered at the time of insertion is striking, but is consistent with previous reports.[9] This suggests, as is reported in the narratives of some reports, that the IUD position is considered normal, sometimes verified by ultrasound, at the time of insertion or during a follow-up visit. It is possible that displacement of the IUD through the damaged uterine wall may take place at a later time. It has been suggested that partial perforation during insertion can result in transmigration over time.[12] However, it is also possible that most perforations occur at the time of insertion but are not detected at the time. In the majority of patients it took about 2 months before the first symptoms were reported. Abdominal pain and findings during routine visits, followed by changes in bleeding pattern, were the

Health professionals are encouraged to:

- ensure they are familiar with and/or trained on the correct insertion technique for Mirena®, and to carefully review the insertion instructions included in the labelling;
- consider performing ultrasound or x-ray imaging in case of a difficult insertion, if patients complain of pain, or if there is suspicion that the system may not be correctly positioned;
- follow up patients 4–12 weeks after insertion, and once a year thereafter or more frequently, as required;
- inform patients before the procedure about the risk of uterine perforation, especially in the post-partum period and during lactation, and educate them on possible signs of this complication, including, but not limited to, severe low abdominal pain, which may be associated with bleeding after the procedure. Advise the patient how to self-check the removal threads of Mirena®

Fig. 1. Advice to professionals in Dear Health Care Professional Letter of Health Canada.[14]

earliest triggers as well as the most common reasons to detect uterine perforations in this study.

Parity, Postpartum Time and Breastfeeding

In the literature, a doubled rate of insertion problems with IUDs is reported in nulliparous women compared with parous woman.[24,25] These problems include pain on insertion, cervical problems and bradycardias, but information on uterine perforations has been limited. In our case series, no conclusions can be drawn on parity as a risk factor for perforation because the proportion of nulliparous women receiving a successful IUD insertion is unknown.

The summary of product characteristics recommends a minimal time for postpartum insertion of 6–12 weeks, depending on the involution of the uterus. In 95% of the cases in which the insertion was postpartum and the postpartum time was reported, the time after delivery was more than 6 weeks.

In the literature, breastfeeding is considered a risk factor for uterine perforation because of low serum estrogen levels and therefore a more contracted and hence smaller uterus.[26] However, others have reported fewer insertion problems during the lactation phase because of higher β-endorphin levels, resulting in lower pain perception.[27] More research is needed on this aspect of LNG-IUD use.

Conclusions

Uterine perforation is a possible complication of the insertion of a LNG-IUD and precautions, as illustrated in figure 1, are necessary. The cases reported in this paper show that a considerable number of women have experienced uterine perforation after insertion of a LNG-IUD, which may impose a risk for these women. The number of cases reported from these four countries is likely to be an underestimate due to underreporting. Comparisons between countries are difficult due to different reporting systems and differences in practice. Our data do not permit calculations of incidence of uterine perforation with the LNG-IUD as the exposed population is not known.

In this case series, many perforations remain undetected for a long time. Vigilance is advised in women with IUDs presenting with abdominal pain or changes in bleeding patterns.

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