



Intrauterine contraceptives: Levonorgestrel Intrauterine Delivery Systems – Mirena and Jaydess Update on risk of uterine perforation

26th February 2016

Dear Healthcare Professional,

In agreement with the HPRA, this letter is to remind you of risk factors for uterine perforation including an update on findings from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD). This was a large prospective, comparative, non-interventional cohort study of intrauterine contraception (IUC), including the copper intrauterine device (IUD) and levonorgestrel intrauterine delivery system (LNG-IUS).

Summary

- The EURAS-IUD study showed:
 - The observed rate of uterine perforation with IUCs was low, occurring in approximately 1 in every 1000 insertions.
 - The most important risk factors for uterine perforation were breastfeeding at the time of insertion and insertion in the 36 weeks after giving birth, regardless of the type of IUC inserted (see Table 1).
 - A high contraceptive effectiveness was demonstrated for all IUCs. The pregnancy rate (including ectopic pregnancy) of LNG-IUS with initial release rate of 20mcg/24 hours was found to be significantly lower than that of Copper IUDs. The study reaffirms the positive benefit-risk profile of IUCs.
- Before inserting IUC, inform women that perforation occurs in approximately 1 in every 1000 insertions and that the symptoms include:
 - severe pelvic pain after insertion (worse than period cramps)
 - not being able to feel the threads
 - pain or increased bleeding after insertion which continues for more than a few weeks
 - sudden changes in periods
 - pain during sex
- Explain to women how to check their threads and tell them to return for a check-up if they cannot feel them (especially if they also have significant pain).
- Partial perforation may have occurred even if the threads can still be seen; consider this if there is severe pain following insertion and perform an ultrasound.

Further information

Intrauterine contraception includes the copper intrauterine device (IUD) and levonorgestrel-releasing intrauterine system (LNG-IUS). IUC is used for long-term contraception. Some LNG-IUS are also licensed for other gynaecological conditions including:

- heavy menstrual bleeding
- protection from endometrial hyperplasia during oestrogen replacement therapy

Uterine perforation is a complication of many gynaecological diagnostic, therapeutic and other procedures, including placement of IUC. Perforation of the body of the uterus or cervix most often occurs during IUC

insertion, but might not be detected until sometime later, and may decrease the effectiveness of IUC. Such a system must be removed and surgery may be required.

Summary of the EURAS-IUD study:

EURAS-IUD was a large prospective, comparative, non-interventional cohort study of women who use IUC, including LNG-IUS with initial release rate of 20mcg/24 hours LNG-IUS (Mirena) and copper IUD^{1,2}. The primary outcome was uterine perforations.

The EURAS-IUD study was carried out in 6 European countries and included over 61,000 women (>43,000 women using LNG-IUS and >18,000 women using various brands of copper IUDs). The incidence rate of uterine perforation was 1.3 (95% CI: 1.1 - 1.6) per 1000 insertions in the whole study population, with no relevant difference between the study cohorts (1.4 [95% CI: 1.1 - 1.8] per 1000 insertions in the LNG-IUS cohort and 1.1 [95% CI: 0.7 - 1.6] per 1000 insertions in the copper IUD cohort).

The risk of perforation was independently increased in the following instances (see Table 1):

- in women who were breastfeeding (compared with women not breastfeeding) at the time of insertion
- when the IUS or IUD was inserted up to 36 weeks (compared with more than 36 weeks) after giving birth).

These risk factors were independent of the type of IUC inserted.

Table 1: EURAS-IUD: Incidence of perforation per 1000 insertions for the entire study cohort, stratified by breastfeeding and time since delivery at insertion

	Breastfeeding at time of insertion	Not breastfeeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 per 1000 (95% CI: 3.9-7.9, n=6,047 insertions)	1.7 per 1000 (95% CI: 0.8-3.1, n=5,927 insertions)
Insertion > 36 weeks after delivery	1.6 per 1000 (95% CI: 0.0-9.1, n=608 insertions)	0.7 per 1000 (95% CI: 0.5-1.1, n=41,910 insertions)

No serious sequelae, such as bowel or bladder injury, or generalised septicaemia or peritonitis were associated with any of the perforations in the study. The majority of perforations in both the LNG-IUS and copper IUD cohorts presented clinically as pain or bleeding problems. However, in 22.0% of the cases the perforation was found at a routine check-up in apparently asymptomatic women. In both cohorts, more than 50% of the perforations were diagnosed within the first two months after IUC insertion.

Recommendations:

In line with guidance issued by the Faculty of Sexual and Reproductive Health³, counsel women considering long-term contraception on the available options (including LNG-IUSs and IUDs). Inform them of the benefits and risks (e.g. perforation), as well as the signs and symptoms of perforation to watch out for, as per the Patient Information Leaflet.

In case of a difficult insertion (e.g. exceptional pain or bleeding during or after insertion) perform a physical examination and ultrasound immediately to exclude perforation. Physical examination alone (including checking of threads) may not be sufficient to exclude partial perforation, which may have occurred even if the threads can still be seen.

Explain to women how to check their threads and tell them to return for a check-up if they cannot feel them (especially if they also have significant pain), or if they have any other symptoms of perforation (see list in summary above). Remind women that during these check-ups, she should tell the doctor/nurse that she has an IUC (in case he/she was not the person who inserted the device).

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRa Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. Reports of suspected adverse reactions can also be made to Bayer Ltd, contact details below.

Company contact point

For further information, please contact Bayer Ltd, The Atrium, Blackthorn Road, Dublin 18; Tel: +353 1 2999313; Fax: +353 1 2061456; E-mail: info.ireland@bayerhealthcare.com.



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References

- 1) Klaas Heinemann, Suzanne Reed, Sabine Moehner, Thai Do Minh. Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. *Contraception*, 91 (4) (2015): 280–283.
- 2) Klaas Heinemann, Suzanne Reed, Sabine Moehner, Thai Do Minh. Risk of Uterine Perforation with Levonorgestrel-Releasing and Copper Intrauterine Devices in the European Active Surveillance Study on Intrauterine Devices. *Contraception*, 91 (4) (2015): 274–279.
- 3) Faculty of Sexual and Reproductive Health, Guidance on Intrauterine Devices as Long-term Contraception: <http://www.fsrh.org/pdfs/CEUGuidanceIntrauterineContraception.pdf>