

## Use of a frameless LNG-IUS as conservative treatment for a pre-malignant uterine polyp in a premenopausal woman – a case report

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### Abstract

Prevention of progression to invasive carcinoma in patients with a premalignant endometrial lesion using long-term treatment with levonorgestrel (LNG) releasing intrauterine systems (IUS) remains controversial, especially when manifest cellular atypia has been found in the endometrial biopsy specimen. We present a case of a 44-year old premenopausal woman with a premalignant uterine polyp who declined hysterectomy and was followed-up for more than 12 years after the first LNG-IUS was inserted. Endometrial atrophy installed, no pathology was detected and hysterectomy was thereby successfully avoided. The positive experience in this case should encourage further studies as literature data indicate that conservative treatment of premalignant endometrial pathology is a real option with a high success rate for women who have a contra-indication for surgery, refuse the classical approach for personal reasons or want to preserve their fertility.

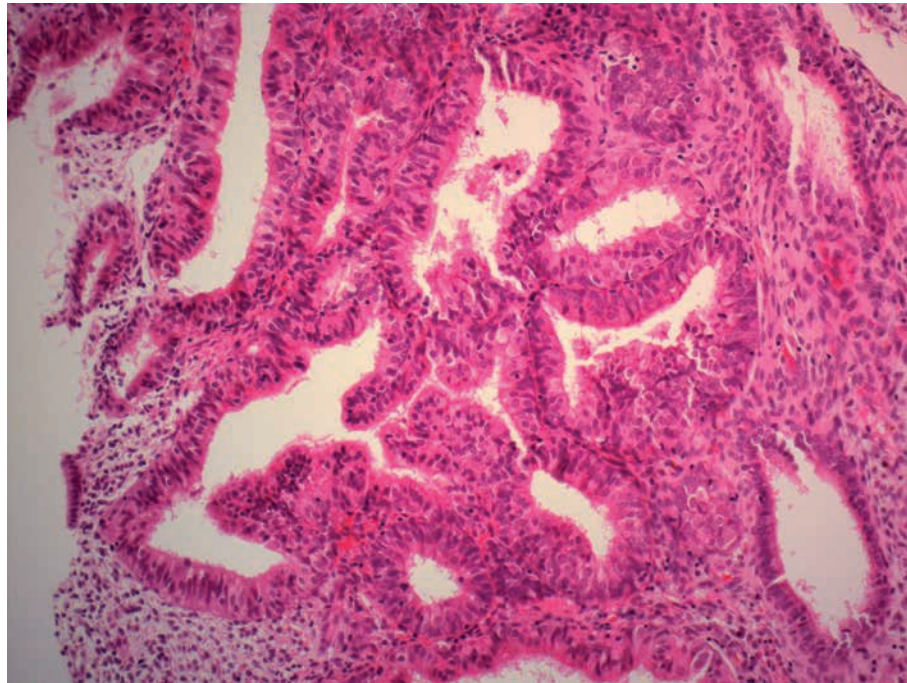
**Key words:** Atypical endometrial hyperplasia, conservative treatment, frameless IUS, levonorgestrel, LNG-IUS, premalignancy.

### Introduction

The levonorgestrel intrauterine system (LNG-IUS), originally developed for long-term contraceptive use, has shown to have a profound effect on the endometrium. The system has been used extensively for the treatment of heavy menstrual bleeding and for the conservative treatment of non-atypical as well as atypical endometrial hyperplasia (Wildemeersch et al., 2003, 2007; Buttini et al., 2009; Baker et al., 2010; Lee et al., 2010; Ørbo et al., 2014) and even for early endometrial adenocarcinoma (Wildemeersch et al., 2010).

During the years 2001-2013 we performed a pilot study on 120 patients with a particular type of LNG-IUS – FibroPlant® (APCOR Research, Belgium) for the conservative management of benign and/or premalignant uterine conditions. Part

of that study concerned the clinical results of 13 patients where endometrial hyperplasia was found after investigative hysteroscopy and D&C, eleven among them showing ‘simple hyperplasia without atypia’, one showing ‘complex hyperplasia without atypia’ while one was diagnosed as a ‘atypical hyperplasia/endometrioid intraepithelial neoplasia’. Benign endometrial polyps were found in another 23 patients (Janssens, 2013). All 36 patients were treated by the insertion of the LNG-IUS, aiming at preventing recurrence or worsening of the endometrial pathology. Informed consent before entering the study had been obtained before receiving the experimental device. Patients were regularly followed-up as appropriate, while avoiding hysterectomy as much as possible. In this report, we describe a patient who presented with ‘atypical hyperplasia’ and treated with LNG-IUS.



**Fig. 1.** — Endometrial sample showing glandular complexity with stratification, loss of polarity, more eosinophilic cytoplasm, nuclear enlargement and atypia (H&E 100×).

### Case report

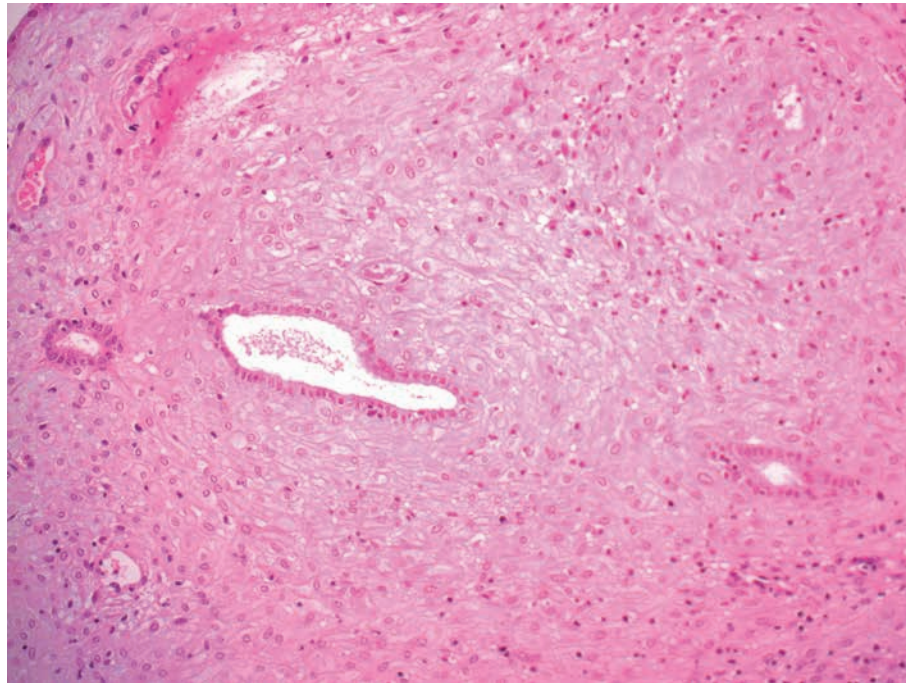
The patient is a 44-year old premenopausal woman who consulted with heavy menstrual bleeding and dysmenorrhea. Pelvic ultrasound revealed a thick irregular endometrium (maximum thickness 22 mm) presumably polypoid, in an otherwise normal uterus. Hysteroscopy revealed a small polyp on the left posterior wall. D&C was performed, removing the polyp. The histological diagnosis of the specimen was atypical hyperplasia/endometrioid intraepithelial neoplasia, with architectural atypia grade 3 and cellular atypia grade 1. Figure 1 illustrates the histological findings. Informed consent was obtained and a FibroPlant® LNG-IUS was inserted and anchored in the uterus in November 2001. Meticulous follow-up was conducted, i. e. including at least a yearly pelvic ultrasound and an endometrial Pipelle (endometrial suction apparatus) biopsy. The first biopsy after LNG-IUS insertion was performed in September 2002. Histopathological examination showed arrested secretion and no evidence of malignancy. In February 2003 and March 2004 new Pipelle samples were taken, showing again arrested secretion, areas of indifferent aspect, suggesting complete regression of atypical hyperplasia. Pelvic ultrasound prior to the biopsy showed a normal uterus with a quasi-atrophic aspect of the endometrium, endometrial thickness less than 3mm and a correctly positioned LNG-IUS. Color-Doppler flow study of the uterine artery showed a

RI (resistance index) of 0.77, as seen normally in the postmenopausal period. Eight months later our patient was referred to a tertiary centre for extensive ultrasound investigation, which confirmed our findings. In September 2006, a new D&C was performed. Hysteroscopy revealed only a discrete irregular aspect at the posterior wall of the uterine cavity. The FibroPlant LNG-IUS was still correctly anchored in the uterine fundus, and easily removed with simple traction. Histopathological investigation showed non-characteristic secretory endometrium and no signs of atypical hyperplasia. Figure 2 illustrates the histopathologic findings in September 2006.

A new FibroPlant LNG-IUS was inserted in October 2006. In September 2009, histological examination showed ‘important decidual transformation, probably hormonally induced’ and the LNG-IUS was replaced for the second time. A last endometrial sample was taken in October 2010, showing ‘chronic non-specific endometritis’. From 2011 until now the patient was followed regularly, showing an atrophic uterus with a LNG-IUS inside. The woman is in amenorrhea since about 10 years and apparently very happy with this treatment and follow-up schedule.

### Discussion

Atypical endometrial hyperplasia, also called ‘adenocarcinoma in situ’, is a well-known precursor



**Fig. 2.** — Endometrial specimen showing extensive decidual change in stroma with few small atrophic glands. No signs of atypical hyperplasia (H&E 100×).

of overt endometrial carcinoma. A rate of 45.9% of endometrial carcinoma was found in hysterectomy specimen in women with this particular subtype of endometrial hyperplasia (Pennant et al., 2008). As was experienced in the observational study we conducted, the malignancy rate associated with endometrial polyps is rather low. Meta-analysis on the oncogenic potential of polyps reveals a malignancy rate between 0.8 and 8% (Lee et al., 2010).

In a recently published prospective Belgian study of 1220 pre-, peri- and postmenopausal women with abnormal uterine bleeding atypical hyperplasia was found in one single patient, i.e. 0.1 % of the total cohort studied, belonging to the post-menopausal group of 454 women (Van den Bosch et al., 2015). Endometrial hyperplasia without atypia was found in 48 patients, about 40 times more frequently. In this perspective, the pre-menopausal patient with atypical endometrial hyperplasia we presented seems a rather exceptional case.

Conservative treatment of atypical endometrial hyperplasia with LNG-IUS can be considered in selected cases, such as in women who wish to preserve their fertility. However, conservative treatment carries an inherent oncologic risk as no correct staging is possible and the risk of missing a concurrent ovarian cancer cannot be neglected. Therefore, patients opting for conservative treatment should have a strict gynaecological follow-up with regular endometrial biopsy and pelvic ultrasound.

Endometrial hyperplasia has been treated before in other centres with LNG-IUS. In an Australian systematic review a 96% regression rate for non-atypical endometrial hyperplasia treated with LNG-IUS was found (Buttini et al., 2009). In their own patient cohort there was (also only) one patient with atypical endometrial hyperplasia, treated with a LNG-IUS for more than seven weeks. The patient had normal endometrial histology on subsequent assessment.

In a Korean study (Lee et al., 2010) complete regression of endometrial hyperplasia was achieved in all 12 cases. In the (also single) case of atypical hyperplasia, the regression was attained at the 9th month after insertion of the LNG-IUS.

A Norwegian research group found LNG-IUS to be effective at reducing the occurrence of hyperplastic endometrial polyps, with effectiveness superior to that of oral progestin and observation-only (Arnes et al., 2014). Furthermore, in the first prospective comparative trial of its kind conducted by the same group, a study was performed to examine the results of the treatment of 170 patients with endometrial hyperplasia which were treated either by an oral progestogen or by LNG-IUS: All 53 women treated with an LNG-IUS showed histologically normal endometrium after 6 months of therapy (Ørbo et al., 2014). In this study nineteen patients were diagnosed with *atypical* hyperplasia and six of them were successfully treated with LNG-IUS. The authors concluded that cyclical

progestogens are found to be less effective compared with continuous oral therapy and LNG-IUS, and should not be used any more for this indication.

## Conclusion

We present a case of a 44-year old premenopausal woman with a premalignant uterine polyp opting for conservative therapy. Today, 14 years after the start of her treatment, the patient is in good health and very happy with this therapeutic option. Considering the rather limited value of a case-report the positive experience should encourage further studies, especially since recent literature data indicate that conservative treatment of premalignant endometrial pathology is a real option with high success rate in selected women such as patients who want to preserve their fertility, have contra-indications for surgery or refuse hysterectomy.

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