Levonorgestrel-Releasing Intrauterine System (LNG-IUS) as a Therapy for Endometrial Carcinoma

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Abstract:

In our study we present two cases that have been diagnosed as stage I endometrial carcinoma where a Levonorgestrel intrauterine releasing system (LNG-IUS) referred to as Mirena was used as a primary treatment because the standard surgical treatment was deemed to carry an unacceptable risk of death. Histopathology report after therapy showed complete regression of endometrial cancer.

Introduction:

Endometrial cancer is the most common genital tract carcinoma in many Western Countries, with the majority (approximately 75%) of women presenting with stage I disease. Although primary treatment of endometrial cancer with a progestagen intrauterine system is reserved for adjuvant or palliative treatment with unproven efficacy.

Mirena is an effective form of contraception widely used as an intra-uterine device. It has a 32 mm long-shaped plastic frame that holds a reservoir (on the vertical stem) of 52 mg Levonorgestrel mixed with polydimethylsioxane to allow a steady release of 20 micogram of Levonorgestrel per day within the endometrial cavity. It is a widely used form of hormonal contraception that is being increasingly employed also in the conservative management of excessive menstrual blood loss.

Breakthrough bleeding following insertion of the LNG-IUS is most commonly a problem during the first 4–6 months. Several studies have looked at the local effect of Levonorgestrel on the endometrium causing altered morphology and function. These including stroma decidualization, glandular atrophy, metaplasia, inflammatory cell infiltration and hemosiderin deposition in the endometrium. Apart from contraceptive purpose it is also used in the management of idiopathic menorrhagia.

Surgery alone is adequate therapy at an early stage but, some patients may be unsuitable for surgery if they have concurrent conditions that put them at an unacceptable mortality risk. The use of Mirena as primary treatment in these circumstances may be valuable. The system used to deliver progestagen to protect the endometrium from endometrial hyperplasic changes in patient taking tamoxifen or estrogen-only hormone replacement therapy.

We present two cases of patients that have been diagnosed with stage I endometrial carcinoma where a Mirena was used as a primary treatment as the standard surgical treatment was deemed to carry an unacceptable mortality risk.

Case Report:

First Case:

A 63-year-old woman with morbid obesity presented in April 2006 with a history of post-menopausal bleeding. The clinical examination was unrewarding but a transvaginal pelvic ultrasound scan showed an endometrial thickness of 17 mm. The uterus was described as normal size with a normal outline. Both ovaries appeared normal and there was no free fluid in the pelvis; an endometrial biopsy (sampling) revealed a well-differentiated endometrial adenocarcinoma. Unfortunately her treatment options were limited due to her obesity (Body Mass Index=60). Surgery was not considered appropriate because of anesthesia risk, technical difficulty, post-operative infection, DVT, so it was decided to manage her with insertion of Mirena loop.

Second Case:

A 57-year-old woman presented with a history of post-menopausal bleeding. She was referred to the hospital on 13.08.2007 with a histopathology report from her country showing low grade adenocarcinoma. Unfortunately her treatment options were limited due to her obesity (Body Mass Index=60). Surgery was not considered appropriate because of anesthesia risk, technical difficulty, post-operative infection, DVT, so it was decided to manage her with insertion of Mirena loop.
We decided to insert a Mirena loop as in the previous case because there was a risk of operation as the patient had body mass (BMI=54), was diabetic on glucophage, and hypertensive on treatment.

**Follow up:**

Both cases were followed regularly every three months with endometrial biopsy. In the first case histopathology after the first three months showed no evidence of residual carcinoma, hyperplasia or atypia but we advised careful follow up as a papillary synytial metaplasia could be seen in an area adjacent to the endometrial carcinoma. An endometrial sample repeated after three months showed complete regression of the disease with no evidence of hyperplasia or malignancy. This patient has now completed one and half years since the initial diagnosis and has no further postmenopausal bleeding. The last endometrial biopsy showed benign fragments of decidualized endometrial stroma consistent with exogenous progesterone effect and chronic endometritis. No evidence of hyperplasia or malignancy.

**Second Case:**

Endometrial pipette biopsy repeated after three months showed a few fragments of endometrial tissue consisting of inactive endometrial glands embedded within pre-decidualised stroma. There was no evidence of hyperplasia or malignancy. This patient has now finished six months and the last histopathology result showed no evidence of residual malignancy. (Figures 1, 2, 3). As our staging was not based on MRI but on histology reports we could not definitely exclude metastatic disease.

Both patients were fully involved in the decision making process and demanded treatment for their postmenopausal bleeding, accepting the potential problems with Mirena coil. Neither experienced any side effects related to Mirena coil and they had reversion of the endometrial histological changes so they allowed continuation.

Figure 1: Endometriod adenocarcinoma, FIGO Grade 1 (well differentiated) showing the back glands

Figures 2 and 3: Decidualized stroma post therapy with Mirena
Discussion:

The standard treatment of an early stage endometrial cancer is hysterectomy, bilateral salpingo-oophorectomy and staging of the abdomen with or without pelvic lymphadenectomy. The overall unadjusted 5-year survival for stage 1 disease is relatively high at 75%, but women with poor prognostic factors within stage 1 can have survival expectancy as low as 26%.(4)

Levonorgestrel is a progestogen that inhibits the endometrial estrogen receptors, making the endometrium insensitive to circulating oestradiol. The therapeutic effect of Mirena is based mainly on local progestogenic effects in the uterine cavity so, in theory, it could be preferable to other progestogens as it achieves higher levels of concentration in the endometrium than in the plasma. (6) In contrast, J Abu, et al reported a case of endometrial cancer in a young woman of 36 years of age who had LNG-IUS inserted 12 months previously.

The local effect of Mirena would result in the breakthrough bleeding usually experienced by users of LNG-IUS but what is not clear is whether the persistently localized inflammatory effect and the reactive glandular atypia may eventually lead to neoplastic changes within the endometrium in a very small subset of women. This hypothesis is not supported by the recent work of Maruo et al.(11)

Another study by Zalel et al(12) also demonstrated significant reduction in the endometrial thickness following LNG-IUS use. There have been other case series on the successful use of LNG-IUS in the treatment of endometrial carcinoma and hyperplasia in patients who were deemed unsuitable for surgery due to medical problem. (3,13) Others have demonstrated endometrial protective effect of the LNG-IUS in women who are on tamoxifen. (14) The Mirena device has been shown to be much more effective in reversing endometrial hyperplasia compared to oral progestogens.(15)

Conclusion:

The histological reversion of endometrial cancer in our patients is very encouraging. The real role of Mirena in the medical management of selected cases of endometrial cancer and also the advantages over the other progestagens needs a larger number of cases to be studied. Longer follow up times are required to reach more valid conclusions. We advise caution in the investigation of women presenting with irregular uterine bleeding for up to 12 months following the insertion of Mirena and to exclude other co-existent pathology.

The insertion of Mirena remains a safe and effective method of contraception and the non-surgical management of dysfunctional uterine bleeding. Its current use should therefore not be discouraged after proper staging. This report will hopefully add some weight to the use of Mirena in the treatment of endometrial cancer in the future.

References:

5. Phillips G, Graham CT. "The effects of the Levonorgestrel intrauterine system (Mirena Coll) on endometrial morphology".