

Weight-Loss Interventions and Levonorgestrel Intrauterine System Implantation for Early-Stage Endometrial Cancer and Atypical Endometrial Hyperplasia to Reduce Perioperative Risk of Severely Obese Patients

Roze Isono-Taniguchi, Hiroshi Tsubamoto*, Kayo Inoue, Tomoko Ueda, Shinichiro Saeki, Yumi Takimoto, Yu Wakimoto, Hiroaki Shibahara

Department of Obstetrics and Gynecology, Hyogo Medical University, Nishinomiya, Hyogo, Japan

Abstract

Endometrial cancer (EC) and atypical endometrial hyperplasia (AEH) are associated with obesity, which increases the perioperative morbidity and surgical difficulties in laparoscopic and robotic surgery. Weight-loss interventions (WLIs) are likely to reduce morbidity; however, delayed surgery may cause cancer progression. To minimize the tumor progression, levonorgestrel intrauterine system (LNG-IUS) with minimal side effects was used until the planned surgery. During 2016 and 2021, we conducted preoperative management of WLI using LNG-IUS for seven highly obese women with a body mass index (BMI) ≥ 35 kg/m² who had AEH and EC with Grade 1 and no myometrial invasion on magnetic resonance imaging. In three of the seven patients, the BMI decreased by more than 5. Two patients with AEH achieved remission after LNG-IUS placement and requested conservative management. Five patients with EC underwent laparoscopic hysterectomy, without perioperative complications.

Keywords: Atypical endometrial hyperplasia, endometrial cancer, levonorgestrel intrauterine system, preoperative management, weight-loss interventions

INTRODUCTION

Obesity is the most common risk factor for endometrial cancer (EC) and atypical endometrial hyperplasia (AEH). The current standard of care is laparoscopic or robotic hysterectomy and bilateral adnexectomy. However, patients with severe obesity have an increased perioperative risk, increased surgical difficulty, and multiple comorbidities.^[1] Therefore, weight-loss interventions (WLIs) can be used in the perioperative management to reduce morbidity. However, delayed surgery may cause cancer progression. The levonorgestrel-releasing intrauterine system (LNG-IUS) could be useful in minimizing the progression of tumors

with minimal side effects. LNG is used in patients with Grade 1 EC and AEH who wish to undergo conservative management. LNG-IUS has a similar effect and minimal risk of side effects compared with oral progestins, including medroxyprogesterone acetate (MPA) and megestrol acetate.^[2] Since 2016, we attempted to reduce perioperative risk by WLI with LNG-IUS implementation before surgery. The WLI included health education on diet and exercise, with one-to-one guidance. The WLI protocol for case 1 was established and managed at the Health Science Center, Kansai

Address for correspondence: Dr. Hiroshi Tsubamoto,
Department of Obstetrics and Gynecology, Hyogo Medical University,
Mukogawa 1-1, Nishinomiya, Hyogo 6638501, Japan.
E-mail: tsuba@hyo-med.ac.jp

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Medical University Hospital. The remaining patients were instructed by their outpatient physician at Hyogo Medical University Hospital on appropriate exercise and diet (not a set-diet program). Eligible patients had AEH or EC with endometrioid grade 1 (G1) without myometrial invasion on magnetic resonance imaging. Their body mass index (BMI) was ≥ 35 kg/m².

CASE REPORTS

Case 1

A 53-year-old nulligravida woman with a BMI of 52.2 kg/m² had Hashimoto's disease, angina pectoris, antiphospholipid antibody syndrome, diabetes mellitus (DM), asthma, and obstructive sleep apnea syndrome. She had a history of emergency admission to the cardiovascular disease intensive care unit (ICU) due to unexplained heart failure. She was referred from another department for postmenopausal irregular genital bleeding. She complained of respiratory distress in the supine position and could tolerate the lithotomy position for <5 min. Outpatient aspiration biopsy revealed AEH. Five months after LNG-IUS implantation and WLI, her weight decreased to 100 kg, with a BMI of 38 kg/m², and she was able to lie in the supine position. Outpatient aspiration biopsy revealed no atypical glands. The patient was scheduled for surgery but requested conservative management. No recurrence was observed in the following 6 years, and the LNG-IUS was removed.

Case 2

A 42-year-old nulligravida woman visited a clinic with excessive menstruation. Endometrial cytology showed suspected AEH, and she was referred to our hospital. Her BMI was 40.9 kg/m², and inpatient dilatation and curettage (D and C) under anesthesia revealed AEH. Two months after LNG-IUS implantation and WLI, her endometrium remained thin on the vaginal ultrasound, and outpatient aspiration biopsy revealed no atypical glands or hyperplasia. She requested conservative management. After 18 months, her weight decreased to 84.1 kg, with a BMI of 37.9 kg/m². She had no recurrence in the following 27 months.

Case 3

A 43-year-old nulligravida woman visited a clinic due to hypermenorrhea. Because EC was suspected, she was referred to our hospital. Outpatient endometrial curettage revealed EC G1. Her BMI was 38.1 kg/m², and she had DM, schizophrenia, and scoliosis. LNG-IUS and WLI treatment until surgery was planned. After 2 months, her BMI was 37.5 with mild weight loss. She had a total laparoscopic hysterectomy (TLH) with bilateral salpingo-oophorectomy. No perioperative complications were observed. The surgical specimen revealed G1 and slight myometrial invasion without lymphovascular

space invasion (LVSI). Peritoneal cytology was negative. There was no evidence of disease 21 months later.

Case 4

A 55-year-old primipara woman was referred to our hospital due to postmenopausal genital bleeding and suspected EC. Outpatient aspiration biopsy revealed EC G1. Her BMI was 36.6 kg/m². She had deep vein thrombosis (DVT) in the inferior vena cava (IVC) central to the renal vein due to protein S deficiency. LNG-IUS was inserted, and anticoagulant therapy started with WLI. Outpatient aspiration biopsy of endometrium every 2 months revealed EC. Four months after her initial visit, her BMI decreased to 30.6 (79.5 kg), and she had TLH under anticoagulation because IVC filter implantation was not possible. No perioperative complications were observed. The surgical specimen revealed G1 and no myometrial invasion without LVSI. Peritoneal cytology was negative. There was no evidence of disease 20 months later.

Case 5

A 63-year-old multipara woman had a history of thyroid cancer and transverse colon cancer and had an incisional hernia. A follow-up blood test for colon cancer revealed elevated serum CA19-9, and hysteroscopy and biopsy revealed EC G1. She was referred to our hospital for EC. Outpatient aspiration biopsy confirmed EC G1. She had asthma, and her BMI was 42.3 kg/m². She had a history of smoking 15 cigarettes/day between the ages of 20 and 40 years. Three months after LNG-IUS implantation and WLI, her BMI decreased to 36.2 kg/m². She had TLH and intestinal adhesiolysis. No perioperative complications were observed. The operative specimen showed Grade 1 with more than 1/2 myometrial invasion without LVSI. Peritoneal cytology was negative. She was diagnosed with stage IB. There was no evidence of disease 18 months later.

Case 6

A 41-year-old nulligravida woman was referred to our hospital for irregular genital bleeding. Outpatient aspiration biopsy revealed EC G1. She had a BMI of 47 kg/m², hypertension (HT), bipolar disorder, primary aldosteronism, adrenal tumor, and asthma. She had a history of smoking 15 cigarettes/day for 20 years. After 3 months of LNG-IUS implantation, WLI with smoking guidance was conducted, and she had a BMI of 46.4 kg/m². She did not quit smoking. She had TLH without perioperative complications. The surgical specimen revealed G1 and no myometrial invasion without LVSI. Peritoneal cytology was negative. She has been alive for 15 months without any lesions.

Case 7

A 48-year-old primipara woman visited a clinic for persistent irregular genital bleeding. Outpatient aspiration biopsy of

the endometrium revealed AEH, and she was referred to our hospital. Inpatient D and C revealed EC G1. She had a BMI of 41.2 kg/m² and complications of HT and DM. She had a history of conization. Three months after LNG-IUS implantation and WLI, her weight was not changed and she underwent TLH. No perioperative complications were observed. The surgical specimen revealed G1 and no myometrial invasion, without LVSI. Peritoneal cytology was negative. There was no evidence of disease 13 months later.

The characteristics of the seven patients described above are summarized in Table 1.

DISCUSSION

During 2016 and 2021, two patients with AEH and five with EC were treated with LNG-IUS and WLI. All patients had multiple comorbidities: DM in four, HT in three, psychiatric disorders in two, and antiphospholipid antibody syndrome in two. One patient had smoking, asthma, and postoperative colorectal cancer. The maximum/minimum/median values for age, weight, and BMI were 63, 41, and 48 years; 137, 89.6, and 100.7 kg; and 52.2 kg/m², 36.6 kg/m², and 41.2 kg/m², respectively. Three patients lost >5 kg/m² of BMI. Laparoscopic surgery was performed in five patients, with an operating time of 3–4 h and blood loss ranging from a small amount to 185 ml. All patients were admitted to the ICU after surgery and discharged 5 days later without perioperative complications.

In highly obese patients, laparoscopic surgery has been reported to be superior to open surgery because of significantly lower postoperative complications, wound complications, blood transfusion rates, and shorter hospital stays compared to open surgery. In a systematic review of laparoscopic surgery for EC, obese patients (BMI >30 kg/m²) tended to

have increased blood loss compared with normal-weight patients.^[3] In addition, as the BMI increased, the rate of laparotomy transition tended to increase. Patients with severe obesity are at high risk for complications such as HT, DM, sleep apnea, chronic obstructive pulmonary disease, and DVT.^[4] Our patient also had multiple comorbidities and was operated on in cooperation with other departments. Postoperative complications have also been shown to increase significantly with increasing BMI.^[3] In particular, it has been reported that open surgery is associated with increased antibiotic use, a significant increase in infectious wound complications, and a significantly higher incidence of venous thrombophlebitis.^[5] Perioperative complications can adversely affect recovery, and efforts should be made to minimize complications.^[6] Imai *et al.*^[7] reported preoperative weight reduction in patients with EC. Sixteen hospitalized patients received the program for approximately 3 weeks, and their weight was reduced by an average of 6.5%. We achieved a longer intervention period through weight loss by administering LNG-IUS.

The WLI with LNG-IUS was conducted as a presurgery preparation treatment. However, two patients (cases 1 and 2) did not undergo surgery because the endometrial neoplasm regressed with LNG-IUS treatment. For Grade 1 EC and AEH patients who desired future fertility or who were at high risk of surgical complications due to severe medical comorbidities, the use of oral administration of high-dose progestins and/or LNG-intrauterine device (LNG-IUD) have been reported. Systemic therapy with high-dose progestins has demonstrated multiple adverse events such as weight gain and thrombosis.^[2] LNG-IUS releases a higher concentration of progestin in the endometrium than in the plasma, which inhibited the proliferation of endometrial

Table 1: Characteristics of patients who had levonorgestrel intrauterine system implantation and weight-loss interventions for preoperative risk reducing management

Case	Age	Diagnosis	Medical history	BMI at diagnosis	BMI after WLI	Reduction of BMI after WLI	Operation	Postsurgical diagnosis	Follow up period (months)	Current status
1	53	AEH	Hashimoto's disease, angina pectoris, antiphospholipid antibody syndrome, DM, asthma, OSAS	52.2	38	-14.2	None	-	72	NED
2	42	AEH	DM	40.9	37.9	-3.0	None	-	27	NED
3	43	G1	DM, schizophrenia, scoliosis	38.1	37.5	-0.6	TLH	G1 IA	21	NED
4	55	G1	DVT, protein S deficiency	36.6	30.6	-6.0	TLH	G1 IA	20	NED
5	63	G1	Asthma	42.3	36.2	-6.1	TLH	G1 IB	18	NED
6	41	G1	HT, bipolar disorder, primary aldosteronism, adrenal tumor, asthma, smoking	47	46.4	-0.6	TLH	G1 IA	12	NED
7	48	G1	HT DM	41.2	41.2	0.0	TLH	G1 IA	10	NED

BMI: Body mass index, WLI: Weight-loss interventions, AEH: Atypical endometrial hyperplasia, G1: Grade 1, DM: Diabetes mellitus, OSAS: Obstructive sleep apnea syndrome, DVT: Deep vein thrombosis, HT: Hypertension, TLH: Total laparoscopic hysterectomy, IA: Stage IA, IB: Stage IB, NED: No evidence of disease

neoplasm. A meta-analysis showed similar regression rate between LNG-IUD and oral administration of MPA.^[8] In a retrospective study of LNG-IUD, overall response rate at 6 months was 67% in Grade 1 EC and 75% in AEH.^[9] In a prospective phase II study by Westin *et al.*, the response rate after 12 months of LNG-IUD implementation was 67% for Grade 1 EC and 90.6% for AEH.^[10] Janda *et al.* conducted a phase II study of LNG-IUD for Grade 1 EC and AEH and demonstrated pathological complete response at 6 months of 67% and 61% among patients who received LNG-IUD with and without WLI, respectively.^[11]

In conclusion, we have attempted to reduce the perioperative risk of WLI with LNG-IUS implantation. We plan to standardize the diet program and validate it in a prospective study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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