Gynecologic Oncology Reports 52 (2024) 101357

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Successful fertility preservation in stage II endometrial carcinoma with long-term progestin therapy: A case report

Yuki Kashihara [a,b,*], Kentaro Sekiyama [a], Akiko Abe [a], Akitoshi Yamamura [b], Yuki Kozono [a], Akiko Okuda [a], Yumiko Yoshioka [a], Toshihiro Higuchi [a]

[a] Department of Obstetrics and Gynecology, Medical Research Institute KITANO HOSPITAL, PIIF Tazuke-kofukai, Osaka, Japan
[b] Department of Gynecology and Obstetrics, Kyoto University Hospital, Kyoto, Japan

ARTICLE INFO

Keywords:
Uterine cancer
Endometrioid carcinoma
Fertility-sparing treatment
Medroxyprogesterone acetate
Ki-67 index

ABSTRACT

Progestin therapy is a fertility-sparing treatment option for well-differentiated stage IA endometrioid carcinomas without myometrial invasion. Here, we present a case of successful pregnancy and live birth following long-term progestin therapy in a patient with stage II well-differentiated endometrioid carcinoma.

A 30-year-old nulliparous woman with an unremarkable medical history presented with abnormal uterine bleeding. A 45 mm mass was identified in the lower uterine segment. An endometrial biopsy revealed grade 1 endometrioid carcinoma, leading to a diagnosis of stage II uterine corpus cancer based on hysteroscopic findings. The patient refused surgical treatment and underwent oocyte retrieval and cryopreservation at another hospital. A subsequent endometrial biopsy revealed a marked reduction in the Ki-67 index from approximately 60 % to less than 10 %, suggesting the possibility of a hormone-sensitive tumor. The patient persistently refused surgery. Therefore, progestin therapy with medroxyprogesterone acetate (MPA) at a dose of 400 mg/day was initiated as a temporary measure until the patient would accept surgery. The tumor gradually reduced in size and eventually disappeared after 9 months. The MPA therapy was discontinued uneventfully after 20 months. Sixteen months after the discontinuation of MPA therapy, atypical endometrial hyperplasia was detected, and a second round of MPA therapy was initiated. Progestin retreatment was successful and was discontinued at 6 months. Four years after the initial treatment, the patient achieved pregnancy through timed intercourse and delivered a healthy baby at 38 weeks of gestation.

1. Introduction

Endometrial cancer predominantly occurs in postmenopausal women. On the other hand, premenopausal women under the age of 40 years account for 2–14 % of patients with endometrial cancer. In Japan and other emerging countries, the incidence of endometrial cancer is rapidly increasing owing to lifestyle changes (Ushijima, 2009). Furthermore, the number of endometrial cancer patients wishing for fertility preservation is also rapidly increasing owing to the trend of delayed marriage and pregnancies. According to data from the Ministry of Health, Labor, and Welfare, Japan, the average age at first marriage and first delivery in 2019 was 29.6 and 30.7 years of age, which is 4.3 and 4.4 years older than in 1980, respectively (Vital Statistics of Japan, 2019). Progestin therapy, as a fertility-preserving treatment, can be selected for patients with grade 1 endometrioid carcinoma (De Rocco et al., 2022; Gunderson et al., 2012), while the indications generally remain limited to stage IA without myometrial invasion (Abu-Rustum et al., 2023; Yamagami et al., 2020). Therefore, patients' wishes for fertility preservation are not always met, and total hysterectomy is inevitable in an increasing number of endometrial cancer cases in younger age.

No method has been established for predicting response to progestin therapy in endometrial cancer patients. Ki-67 has been used as a marker of cell proliferation to predict the prognosis in various cancers. MPA acts on progesterone receptors (PR)-expressing endometrioid carcinoma by suppressing the growth of cancer cells through PR, and Ki-67 expression is reportedly reduced by MPA therapy (Kashima et al., 2009).

In this report, we present a case of stage II endometrial cancer that resolved with progestin therapy with medroxyprogesterone acetate (MPA), which resulted in long-term remission followed by the birth of a baby. In addition, we highlighted the possible significance of a decrease in the Ki-67 index early in MPA exposure for predicting response to

* Corresponding author at: Department of Gynecology and Obstetrics, Kyoto University Hospital, 54 Shogoin-kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: k.ashi.yobukkgyiinn24@gmail.com (Y. Kashihara).

https://doi.org/10.1016/j.gore.2024.101357
Received 25 January 2024; Received in revised form 24 February 2024; Accepted 28 February 2024
Available online 29 February 2024

progestin therapy.

2. Case presentation

A 30-year-old nulliparous woman (height, 142 cm; Body Mass Index, 24.3 kg/m) presented to a previous hospital with the chief complaint of persistent uterine bleeding lasting for more than a year. There were no significant family or medical histories. She did not have the risk factors for endometrial cancer. Her menstrual cycle was regular without dysmenorrhea and hypermenorrhea. Imaging revealed a mass extending from the endocervix to the lower uterine segment. Endometrial aspiration biopsy revealed adenocarcinoma, leading to a diagnosis of cervical adenocarcinoma and a recommendation for curative surgery. The patient sought a second opinion and visited three other medical institutions before being referred to our hospital.

During the initial examination in our department, colposcopy did not reveal any lesions in the cervix. Internal examination revealed good uterine mobility, and no palpable nodules were detected in the parametrium upon rectal examination. Blood tests revealed no significant abnormalities in the complete blood count or biochemical profile. The CA125 and CA19-9 levels were slightly elevated to 41 U/mL, and 73.3 U/mL, respectively. Squamous cell carcinoma-associated antigen (SCC) was 0.5 ng/mL, which was within the reference limits. Magnetic resonance imaging (MRI) of the pelvis revealed a 45-mm mass with a moderate T2-weighted signal and restricted diffusion that spread from the endocervix to the lower uterine segment with myometrial invasion (Fig. 1). Additionally, T2-weighted images showed a stromal ring defect suggestive of cervical stromal invasion. Positron emission tomography-computed tomography revealed no lymph nodes or distant metastases. Based on the imaging findings, both cervical and endometrial cancers were considered as differential diagnoses.

An initial endocervical curettage biopsy showed the proliferation of atypical glandular cells with a confluent glandular or cribriform pattern, consistent with grade 1 well-differentiated endometrioid carcinoma (Fig. 2). Immunohistochemistry revealed that Ki-67-positive cells were observed in approximately 60 %, vimentin was generally positive, and estrogen receptor was partially positive. The molecular classification of the tumor was not available. Hysteroscopy revealed a broad-based exophytic lesion with atypical vessels in the lower uterine segment. No obvious tumors were observed in the endocervix. Based on imaging, pathological diagnosis, and hysteroscopic findings, the patient was diagnosed with clinical stage II uterine corpus cancer (FIGO 2008) and was deemed suitable for curative surgery.

Due to her strong desire for fertility preservation, the patient refused surgery. Prior to hysteroscopy, the patient underwent oocyte retrieval and cryopreservation using Progestin-primed Ovarian Stimulation (PPOS) at another hospital. The PPOS protocol involved 300 International Unit (IU) of Human Menopausal Gonadotrophin (HMG) and 10 mg of MPA for nine days, starting on the 9th day of the menstrual cycle. Oocyte retrieval used hCG 3000 IU as a trigger. A subsequent endocervical biopsy revealed a marked reduction in Ki-67-positive cells (Fig. 3), suggesting the possibility of a hormone-sensitive tumor.

The patient was informed that fertility-sparing treatment was not indicated and that radical surgery was recommended for stage II uterine corpus cancer. However, the patient refused surgery; therefore, progestin therapy was initiated as a temporary measure until the patient would accept surgery. Pelvic MRI and endometrial biopsy were performed monthly and every three months, respectively.

Progestin therapy with MPA was initiated at a dose of 400 mg/day. After two months, the tumor had significantly reduced to 30 mm in size on MRI. Endometrial biopsy after three months showed a decrease in the number of atypical glandular cells and Ki-67-positive cells. Nine months later, hysteroscopy, and endometrial biopsy revealed no lesions. After genetic counseling, the patient underwent germline genetic testing for Lynch syndrome genes only, which ruled out Lynch syndrome. Due to the lack of established guidelines on the optimal duration of MPA therapy for stage II uterine corpus cancer, we decided to continue MPA therapy for over one year following the patient's achievement of a complete response. At 20 months, CT and MRI did not reveal any residual or recurrent lesions. Concurrently, the patient expressed her intention to conceive with her partner in near future. In response to her request, we decided to temporarily suspend her treatment to assess the risk of short-term recurrence. Meanwhile, strict follow-up was performed. Cervical cytology and transvaginal ultrasound were repeated monthly. Endometrial biopsy was performed every few months. CT or MRI was obtained every three months.

Sixteen months after discontinuation of MPA therapy, MRI revealed a suspicious lesion in the anterior wall of the lower uterine segment.

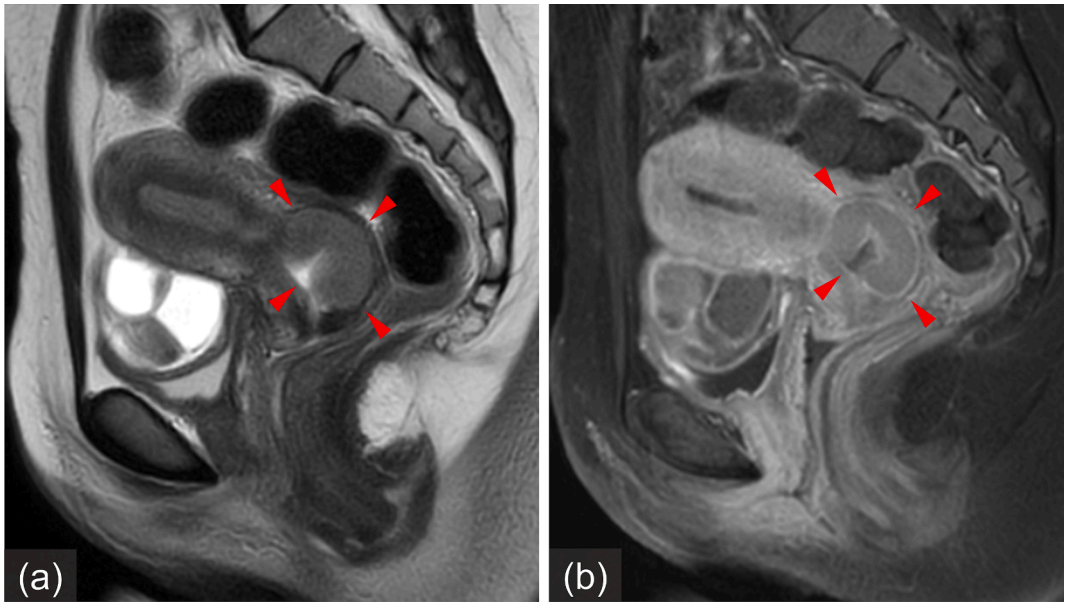

Fig. 1. Magnetic Resonance Imaging (MRI) of the pelvis at the initial examination. (a) A 45-mm mass with moderate signal intensity on T2-weighted imaging spreading from the endocervix to the lower uterine segment (red arrowheads). (b) Contrast-enhanced MRI image showing marginal contrast enhancement (red arrowheads). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

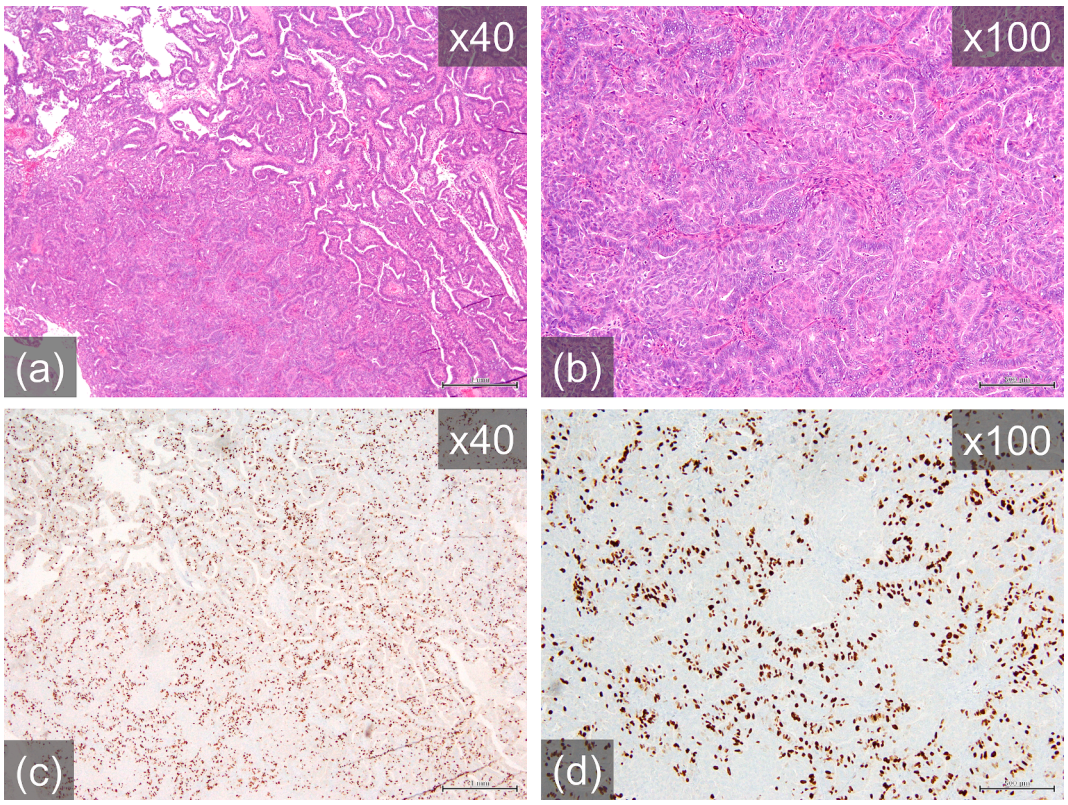

Fig. 2. Histopathology of the initial endocervical curettage biopsy. Hematoxylin and eosin (HE) staining showed a proliferation of atypical glandular cells (×40) (a), grade 1 well-differentiated endometrioid carcinoma, with a confluent glandular pattern (×100) (b). Immunohistochemistry showed the tumor cells positive for Ki-67 (×40) (c) and these were approximately 60% (×100) (d).

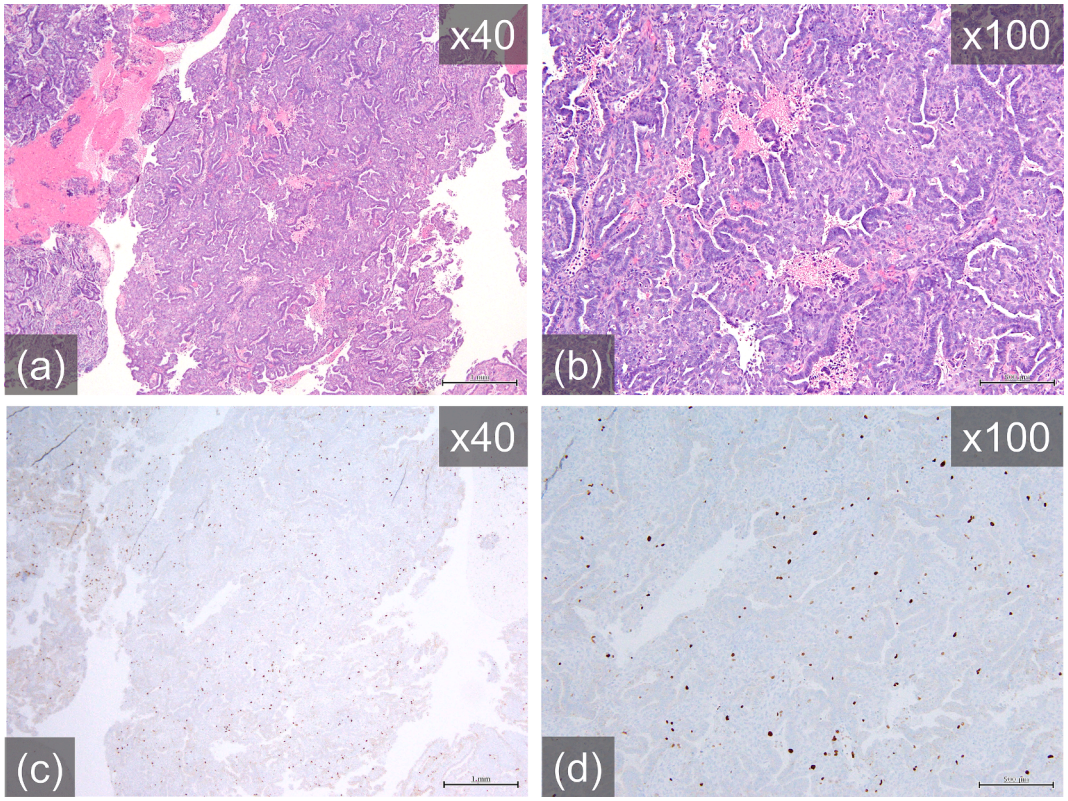

Fig. 3. Histopathology of the endometrial curettage after oocyte retrieval. The dense proliferation of glandular epithelium was shown (HE ×40) (a). Fused glands are observed, and the stroma is still preserved (HE ×100) (b). Compared to the initial biopsy specimen, there was a minimal presence of Ki-67-positive cells (×40) (c), scattered at a level of less than 10% (×100) (d).

Hysteroscopy revealed an exophytic mass in the lower uterine segment, and an endometrial biopsy confirmed atypical endometrial hyperplasia. Because the patient was married, she requested fertility preservation and could not accept surgical intervention. A second MPA therapy was initiated at the same dose. Hysteroscopic biopsy at two months and MRI at four months revealed resolution of the lesion. Since subsequent hysteroscopic biopsy and CT showed no endometrial lesions or metastases at six months, MPA therapy was discontinued, and pregnancy was permitted. The patient achieved pregnancy through timed intercourse 3 months later, four years after the start of the initial treatment. MRI at 20 and 34 weeks of gestation confirmed no recurrence, and an elective cesarean section was performed because of cephalopelvic disproportion at 38 weeks of gestation. Despite a history of frequent endometrial curettage, no evidence of placenta accreta was found and no apparent lesions were observed in the lower uterine segment. An endometrial biopsy was performed on the posterior wall of the lower uterine segment during cesarean section, and no atypical glands were found. MRI at six months postpartum showed no signs of recurrence.

3. Discussion

This case report highlights the following two points: First, fertility preservation can be achieved with long-term MPA therapy even in stage II uterine corpus cancer under strict monitoring. Second: a decrease in Ki-67-positive tumor cells early after MPA exposure may predict the efficacy of MPA therapy.

Fertility preservation can be achieved with progestin therapy in well-differentiated endometrial cancers, although progestin therapy is not recommended for stage II uterine cancer (Abu-Rustum et al., 2023; Yamagami et al., 2020). The response rate to progestin therapy using MPA has been reported to be approximately 53–92 %, with a recurrence rate of 11–53 % (Fujiwara et al., 2012). Fujiwara et al. (2012) retrospectively investigated the outcomes of MPA therapy in 59 patients with endometrial cancer. The complete response (CR) rate was 71 % (42 cases), and recurrence was observed in 52 % (22 cases). When comparing the outcomes of MPA therapy between stages IA and IB–IIA (FIGO 1988), significant differences were observed in CR rates of 80.0 % and 42.9 % ($p < 0.01$), respectively, whereas the recurrence rates were 47.2 % and 83.3 % ($p = 0.11$), respectively. It is possible the MRI overcalled the cervical stromal involvement. The sensitivity, specificity and diagnostic accuracy rates of contrast-enhanced magnetic resonance imaging (CE-MRI) were reported 45 %, 91.2 %, and 85.6 % respectively for cervical stromal involvement (Teng et al., 2015). Cervical invasion is detected as disruption of the low-signal intensity of the inner cervical stroma on T2-weighted imaging and/or disruption of the cervical epithelium enhancement on CE-MRI. Because both features were confirmed in this case, we diagnosed the patient as stage II clinically. Based on previously published results, the National Comprehensive Cancer Network Guidelines for Uterine Neoplasms (Abu-Rustum et al., 2023) and the Japan Society of Gynecologic Oncology guidelines for the treatment of uterine body neoplasm (Yamagami et al., 2020) only recommended MPA therapy for stage IA uterine corpus cancer. However, our report implies that even patients with stage II uterine corpus cancer can achieve complete remission and have a baby after receiving long-term MPA therapy under strict monitoring. In this case, recurrence of atypical endometrial hyperplasia was observed after discontinuation of the first MPA therapy; however, the patient successfully delivered a baby after the second MPA therapy. Progestin retreatment in patients with recurrent endometrial lesions after successful initial progestin therapy has been reported to be effective and safe (Park et al., 2013). The ESGO/ESTRO/ESP guidelines (2021) state that fertility preservation therapy for recurrent endometrial lesions should be administered under strict management in selected cases (Concin et al., 2021).

A decrease in Ki-67-positive tumor cells early after MPA exposure may predict the efficacy of MPA therapy. Early prediction of treatment efficacy at the beginning of MPA therapy would be useful, although endometrial curettage is usually performed 3 and 6 months after treatment initiation to confirm remission. Ki-67 immunostaining is commonly used to assess the proliferative activity of tumor cells and is associated with the prognosis of various cancers. The Ki-67 index is reportedly useful for predicting the prognosis of MPA therapy in patients with recurrent and progressive endometrial cancer patients (Yunokawa et al., 2017). MPA acts on progesterone receptors (PR)-expressing endometrioid carcinoma by suppressing the growth of cancer cells through PR. Ki-67 expression is reportedly reduced by MPA therapy (Kashima et al., 2009), while the relationship between changes in the Ki-67 index early after MPA exposure and treatment response is unknown. In this case, the percentage of Ki-67-positive tumor cells decreased from 60 % to less than 10 % early after MPA exposure, suggesting that changes in the Ki-67 index predict the treatment response and subsequent efficacy.

Although progestin therapy is not recommended for stage II endometrial cancer due to its high rate of failure, our case suggest that fertility preservation could be possible under case selection and strict monitoring. The molecular classification has been introduced for endometrial cancer in the FIGO classification, leading to the advancement of tailored medicine for individual patients (Berek et al., 2023). In the future, it is anticipated that knowledge will accumulate regarding cases where progestin therapy is effective.

Ethical approval

All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Yuki Kashihara: Writing – review & editing. **Kentaro Sekiyama:** Writing – review & editing, Writing – original draft, Project administration. **Akiko Abe:** Writing – review & editing. **Akitoshi Yamamura:** Writing – review & editing, Data curation. **Yuki Kozono:** Writing – review & editing. **Akiko Okuda:** Writing – review & editing. **Yumiko Yoshioka:** Writing – review & editing. **Toshihiro Higuchi:** Writing – review & editing, Supervision.

References

Abu-Rustum, N., Yashar, C., Arend, R., Barber, E., Bradley, K., Brooks, R., et al., 2023. Uterine neoplasms, version 1.2023, NCCN clinical practice guidelines in oncology. J. Natl. Compr. Canc. Netw. 21, 181–209. https://doi.org/10.6004/jnccn.2023.0006.

Berek, J.S., Matias-Guiu, X., Creutzberg, C., Fotopoulou, C., Gaffney, D., Kehoe, S., et al., 2023. FIGO staging of endometrial cancer: 2023. Int. J. Gynaecol. Obstet. 162, 383–394. https://doi.org/10.1002/ijgo.14923.

Concin, N., Matias-Guiu, X., Vergote, I., Cibula, D., Mirza, M.R., Maenitz, S., et al., 2021. ESGO/ESTRO/ ESP guidelines for the management of patients with endometrial carcinoma. Int. J. Gynecol. Cancer 31, 12–39. https://doi.org/10.1136/ijgc-2020-002230.

De Rocco, S., Buca, D., Oronzii, L., Petrillo, M., Fanfani, F., Nappi, L., et al., 2022. Reproductive and pregnancy outcomes of fertility-sparing treatments for early-stage endometrial cancer or atypical hyperplasia: a systematic review and meta-analysis. Eur. J. Obstet. Gynecol. Reprod. Biol. 273, 90–97. https://doi.org/10.1016/j.ejogrb.2022.04.019.

Fujiwara, H., Jobo, T., Takei, Y., Saga, Y., Imai, M., Arai, T., et al., 2012. Fertility-sparing treatment using medroxyprogesterone acetate for endometrial carcinoma. Oncol. Lett. 3, 1002–1006. https://doi.org/10.3892/ol.2012.602.

Gunderson, C.C., Fader, A.N., Carson, K.A., Bristow, R.E., 2012. Oncologic and reproductive outcomes with progestin therapy in women with endometrial

hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol. Oncol. 125, 477–482. https://doi.org/10.1016/j.ygyno.2012.01.003.

Kashima, H., Horiuchi, A., Uchikawa, J., Miyamoto, T., Suzuki, A., Ashida, T., et al., 2009. Up-regulation of nuclear receptor corepressor (NCoR) in progestin-induced growth suppression of endometrial hyperplasia and carcinoma. Anticancer Res. 29, 1023–1029.

Park, J.Y., Lee, S.H., Seong, S.J., Kim, D.Y., Kim, T.J., Kim, J.W., et al., 2013. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol. Oncol. 129, 7–11. https://doi.org/10.1016/j.ygyno.2012.12.037.

Teng, F., Zhang, Y.F., Wang, Y.M., Yu, J., Lang, X., Tian, W.Y., et al., 2015. Contrast-enhanced MRI in preoperative assessment of myometrial and cervical invasion, and lymph node metastasis: diagnostic value and error analysis in endometrial carcinoma. Acta Obstet. Gynecol. Scand. 94, 266–273. https://doi.org/10.1111/aogs.12570.

Ushijima, K., 2009. Current status of gynecologic cancer in Japan. J. Gynecol. Oncol. 20, 67–71. https://doi.org/10.3802/jgo.2009.20.2.67.

Vital Statistics of Japan, 2019. The Ministry of Health, Labor, and Welfare, https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf (accessed 22 February 2024).

Yamagami, W., Mikami, M., Nagase, S., Tabata, T., Kobayashi, Y., Kaneuchi, M., et al., 2020. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J. Gynecol. Oncol. 31, e18.

Yunokawa, M., Yoshida, H., Watanabe, R., Noguchi, E., Shimomura, A., Shimoi, T., et al., 2017. Allred score is a promising predictor of prognosis and medroxyprogesterone acetate efficacy in patients with endometrial cancer. Cancer Chemother. Pharmacol. 80, 127–134. https://doi.org/10.1007/s00280-017-3342-5.