International Journal of Clinical Oncology (2023) 28:587–591
https://doi.org/10.1007/s10147-023-02297-y

ORIGINAL ARTICLE

Obstetric outcomes after medroxyprogesterone acetate treatment for early stage endometrial cancer or atypical endometrial hyperplasia: a single hospital-based study

Maki Oishi[1] · Yoshifumi Kasuga[1] · Yuka Fukuma[1] · Asuka Hamuro[1] · Junko Tamai[1] · Yuya Tanaka[1] · Keita Hasegawa[1] · Takuma Yoshimura[1] · Satoru Ikenoue[1] · Daigo Ochiai[1,2] · Wataru Yamagami[1] · Mamoru Tanaka[1]

Received: 14 November 2022 / Accepted: 11 January 2023 / Published online: 20 January 2023

Abstract

Background To investigate perinatal outcomes in pregnancy after high-dose medroxyprogesterone acetate (MPA) therapy for early stage endometrial cancer (EC) and atypical endometrial hyperplasia (AEH) and to determine whether pregnancy after MPA therapy is at a higher risk of placenta accreta.

Methods Data of 51 pregnancies in 46 women who received MPA therapy for EC or AEH and delivered after 22 weeks of gestation at Keio University Hospital were reviewed. A retrospective matched case–control study was performed to determine the risk of placenta accreta in pregnancy after MPA therapy compared with singleton pregnancies without any history of maternal malignancy treatments.

Results The incidence of placenta accreta was higher in the MPA group than in the control group (15.7 vs. 0%, $p=0.0058$). However, no differences in other perinatal outcomes were observed between groups. While gestational weeks at delivery in the MPA group were later than those in the control group ($p=0.0058$), no difference in the incidence of preterm delivery was recorded between groups. In the MPA therapy group, the number of patients who underwent ≥ 6 dilation and curettage (D&C) was higher in the placenta accreta group than in the non-placenta accreta group (50.0 vs. 14.0%, $p=0.018$). Patients with ≥ 6 D&Cs demonstrated a 6.0-fold increased risk of placenta accreta ($p=0.043$, 95% CI 1.05–34.1) than those receiving ≤ 3 D&Cs.

Conclusion Pregnancy after MPA therapy is associated with a high risk of placenta accreta. In cases in which the frequency of D&C is high, placenta accreta should be considered.

Keywords Endometrial cancer · Atypical endometrial hyperplasia · Medroxyprogesterone acetate · Placenta accreta · Pregnancy

Introduction

Endometrial cancer (EC) and atypical endometrial hyperplasia (AEH) are occasionally detected in childbearing women [1]. However, since the standard treatment for EC and AEH is hysterectomy, patients diagnosed with these are unable to bear children after treatment. In these cases, high-dose medroxyprogesterone acetate (MPA) therapy can be used as a fertility-sparing treatment for young women with EC or AEH in their early stages [2]. Furthermore, repeated MPA therapy is effective for intrauterine recurrence [3]. Although MPA therapy is a fertility-sparing treatment, we have previously reported that many women needed infertility treatment to conceive thereafter, and disease recurrence, endometrial thickness during ovulation, and age of pregnancy permission influenced infertility [4]. Furthermore, perinatal outcomes are important after MPA therapy, but data regarding perinatal complications on these pregnancies remain limited. Since repeated MPA therapy is sufficiently effective for intrauterine recurrence [3], patients often undergo multiple dilatations and curettage (D&C) to evaluate its effects.

✉ Yoshifumi Kasuga
17yoshi23.k@gmail.com

[1] Department of Obstetrics and Gynecology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-Ku, Tokyo 160-8582, Japan

[2] Department of Obstetrics and Gynecology, School of Medicine, Kitasato University, 1-15-1, Kitasato, Minami-Ku, Sagamihara-Shi, Kanagawa 252-0375, Japan

Considering the association between D&C and perinatal complications, Ota et al. have reported that seven out of ten patients with placenta accreta or increta needed D&C because of artificial or spontaneous abortions [5]. Furthermore, D&C for miscarriage is reportedly a risk factor for abnormally invasive placentation, including placenta accreta, increta, and parcreta [6, 7]. Therefore, the development of placenta accreta in pregnancy after MPA therapy due to D&C has become a concern.

Considering this, this study aimed to investigate perinatal outcomes in pregnancy after MPA therapy for early stage EC and AEH, as well as to determine whether pregnancy after MPA therapy is associated with a higher risk of placenta accreta.

Materials and methods

Patients

Data of 51 pregnancies in 46 women who received MPA therapy for EC or AEH and delivered after 22 weeks of gestation at Keio University Hospital were retrospectively reviewed. Women with twin pregnancies were excluded from the study ($n=2$). MPA therapy was administered as described in our previous report, and it was provided if the following indications applied: (1) diagnosis of AEH or endometrioid carcinoma (EM) G1 by D&C; (2) no myometrial invasion, cervical involvement, or extrauterine lesions diagnosed by magnetic resonance imaging (MRI) and computed tomography (CT); and (3) desire for childbearing [3]. However, three women with EM G2, who had a strong desire for childbearing, received MPA therapy in this study, because the ratio of the solid component was < 10% and nuclear atypia was weak. All patients underwent at least two D&Cs and/or hysteroscopic transcervical resection (TCR) before conception. In our hospital, they are not managed with any particular perinatal care because of pregnancy after MPA therapy. Therefore, the mode of delivery was decided based on obstetric conditions. However, we examined placental pathology after delivery to investigate recurrence. In this study, placenta accreta was defined as manual removal of the placenta, massive postpartum hemorrhage (blood loss > 500 g), or a retained placenta [8].

This study was approved by the Ethics Committee of Keio University School of Medicine (Nos. 20150103 and 20120243).

Statistical analysis

We performed a retrospective matched case–control study to determine the risk of placenta accreta in pregnancy after MPA therapy compared with a control group consisting of singleton pregnancies without any history of maternal malignancy treatments (e.g., MPA therapy, conization, and trachelectomy). The control group was recruited from the perinatal database between 2013 and 2019 at Keio University Hospital ($n=3988$) by propensity score matching (PSM) using the JMP software (ver. 15, SAS Institute, Cary, NC, USA). The score was estimated using a logistic regression model, and greedy matching (ratio of 1:1 and matching without replacement) with a caliper width with a 0.20 standard deviation of the estimated logit was performed. Factors used for PSM were maternal age, parity, and in vitro fertilization and embryo transfer (IVF-ET). Finally, the balance of each covariate between cases and controls was evaluated using standardized differences (between-group difference/pooled standard deviation). An absolute standardized difference value < 10% was considered a relatively small imbalance.

Data are presented as the median (range) or number of cases (percentage). Continuous data were compared between groups using the Mann–Whitney *U* test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Odds ratios (ORs) and their 95% confidence intervals (CIs) for the association between the number of D&Cs and placenta accreta were evaluated using logistic regression analysis. All tests were statistically analyzed using JMP software (ver. 15, SAS Institute, Cary, NC), and statistical significance was established at $p<0.05$.

Results

Oncologic characteristics in pregnant women after MPA therapy

The oncologic characteristics of the MPA group are presented in Table 1. Of the 46 patients, 21 were diagnosed with AEH, 22 with EM G1, and 3 with EM G2. The median number of MPA therapy sessions was 1 (range 1–5), and D&C was 3 (range 2–11). The median total duration to achieve complete response was 6 months (range 1.5–60). None of the patients experienced recurrence due to placental pathology.

Comparison of maternal and obstetrics characteristics between the MPA and control groups

A comparison of maternal and perinatal outcomes between the MPA ($n=51$) and control ($n=51$) groups is presented in Table 2. No placenta increta or percreta was recorded in either group. However, the incidence of placenta accreta was higher in the MPA group than in the control group (15.7 vs. 0%, $p=0.0058$), while no differences in the other perinatal outcomes were observed between groups. While gestational weeks at delivery in the MPA group were later than those in the control group ($p=0.0058$), no difference

Table 1 Oncologic characteristics in MPA therapy group ($n=46$)

	Number or median (range)
Histological type	
Atypical endometrioid hyperplasia	21
Endometrioid carcinoma G1	22
Endometrioid carcinoma G2[a]	3
Number of MPA therapy	1 (1–5)
Number of dilatation and curettage	3 (2–11)
Total duration to achieve complete response (month)	6 (1.5–60)
Number of the patients experienced recurrence due to placental pathology	0

MPA high-dose medroxyprogesterone acetate

[a]Three women with endometrial cancer G2 received MPA therapy in this study, because the ratio of solid component was less than 10% and nuclear atypia was weak

in the incidence of preterm delivery was observed between groups. Furthermore, no differences in birth weight, blood loss at delivery, or incidence of cesarean section (C-section) were observed between groups. In the MPA therapy group, six women developed preterm pregnancy due to preterm premature rupture of membrane (PROM) in breech presentation ($n=2$), abnormal bleeding from placenta previa or low-lying placenta ($n=1$), uterine rupture ($n=1$), and hypertensive disorder of pregnancy (HDP) ($n=1$). Moreover, in the MPA therapy group, two patients developed uterine rupture (preterm and term); prophylactic cerclage could not be removed in one patient, while she was in labor, and another delivered by vacuum-assisted vaginal delivery due to prolonged labor.

Comparison of maternal and perinatal characteristics in the MPA group between the placenta accreta and non-placenta accreta groups

A comparison of the maternal and perinatal characteristics between the placenta accreta and non-placenta accreta groups is presented in Table 3. No differences in maternal age at delivery, pre-pregnancy body mass index (BMI), incidence of nulliparity, IVF-ET, EC, placenta previa, number of MPA therapies, and D&C were observed between groups. However, the number of patients who received ≥ 6 D&Cs was higher in the placenta accreta group than in the non-placenta accreta group (50.0 vs. 14.0%, $p=0.018$). Patients with ≥ 6 D&Cs demonstrated a 6.0-fold increased risk of placenta accreta ($p=0.043$, 95% CI 1.05–34.1) than those who received ≤ 3 D&Cs.

Discussion

Pregnancy after MPA therapy is associated with a high risk of placenta accreta. In particular, patients who underwent ≥ 6 D&Cs before conception were at a higher risk of placenta

Table 2 Comparison of maternal and perinatal characteristics between MPA group and control group

	MPA group ($n=51$)	Control group ($n=51$)	p value
Maternal age at delivery (years)	38 (28–47)	38 (28–47)	1
Pre-pregnancy BMI (kg/m^2)	20.1 (16.6–46.5)	20.7 (16.0–37.5)	0.73
Nulliparity	43 (84.3%)	43 (84.3%)	1
IVF-ET	23 (45.1%)	23 (45.1%)	1
Perinatal complication			
Cervical incompetency	3 (5.9%)	0 (0%)	0.24
Hypertensive disorder of pregnancy	3 (5.9%)	3 (5.9%)	1
Gestational diabetes mellitus	4 (7.8%)	11 (21.6%)	0.09
Placental previa	2 (3.9%)	2 (3.9%)	1
Atonic bleeding	3 (5.9%)	1 (2.0%)	0.62
Placenta accreta	8 (15.7%)	0 (0%)	0.0058
Uterine rupture	2 (3.9%)	0 (0%)	0.50
Gestational weeks at delivery (weeks)	39 (26–41)	38 (24–41)	0.025
Preterm delivery (< 37 gestational weeks)	6 (11.8%)	12 (23.5%)	0.19
Birthweight (g)	2969 (860–3946)	2958 (633–3748)	0.60
Cesarean section	32 (62.8%)	25 (49.0%)	0.23
Bleeding at delivery (g)	850 (209–3352)	895 (202–2643)	0.64

Data were median (range) or *n* (%)

MPA medroxyprogesterone acetate, *BMI* body mass index, *IVF-ET* in vitro fertilization and embryo transfer

Table 3 Comparison of maternal and perinatal characteristics in MPA group between placenta accreta group and non-placenta accreta group

	Placenta accreta group ($n=8$)	Non-placenta accreta group ($n=43$)	p value
Maternal age at delivery (years)	38.5 (35–42)	38 (28–47)	0.20
Pre-pregnancy BMI (kg/m^2)	22.3 (19.8–30.8)	20.1 (16.6–46.5)	0.11
Nulliparity	6 (75.0%)	37 (86.1%)	0.60
IVF-ET	5 (62.5%)	18 (41.9%)	0.44
Endometrial cancer	4 (50.0%)	23 (53.5%)	1
Number of MPA (cycle)	1.5 (1–3)	1 (1–5)	0.16
Number of D&C	5 (2–8)	3 (2–11)	0.06
≥ 6	4 (50.0%)	6 (14.0%)	0.018
Days during MPA therapy (days)	447 (140–967)	164 (91–1792)	0.16
Placental previa	0 (0%)	2 (4.7%)	0.18
Gestational weeks at delivery (weeks)	39 (33–41)	39 (26–41)	0.72
Birthweight (g)	3115 (2276–3946)	2960 (860–3876)	0.17
Bleeding at delivery (g)	1075 (328–1340)	895 (209–3352)	0.31

Data were median (range) or n (%)

MPA medroxyprogesterone acetate, *BMI* body mass index, *IVF-ET* in vitro fertilization and embryo transfer, *D&C* Dilation and curettage

accreta than those who received ≤ 3 D&Cs (OR = 6.0). Since there is a paucity of data on perinatal outcomes of pregnancy after MPA therapy, we considered that our results could provide important information for clinicians and patients after MPA therapy.

When women with EC or AEH receive MPA therapy, some D&Cs should be performed to diagnose and evaluate the effects of treatment. However, an increased number of D&Cs in women with a history of abortion also increases the risk of placenta accreta [6, 7]. In previous reports on pregnancy after MPA therapy, only one small sample size has been reported to have D&Cs and placenta accreta, and no placenta accreta occurred among 10 patients after MPA therapy who underwent 3.5 D&Cs (median, range 3–9) [9]. Because our data were larger than those in this previous report, our information might be more useful. Moreover, because the diagnostic accuracy of each test varies, the risk should be assessed based on clinical information. Therefore, the frequency of D&Cs may be important in predicting the occurrence of placenta accreta in pregnancy after MPA therapy.

Although some clinicians are concerned regarding the recurrence of using hormonal therapy for conception, the safety of IVF-ET has been investigated in a previous report [10]. In our study, 23 patients (45.1%) conceived via IVF-ET, and none of them experienced recurrence. Furthermore, the incidence of preterm delivery after MPA therapy in our data was 11.8%, equal to that of previous data (8.6%) [11]. Although no difference in preterm delivery was identified between the MPA therapy and control groups in this study, the incidence of preterm delivery in the MPA therapy group was higher than that of the general Japanese population (5%). In our cases, preterm delivery with MPA therapy occurred because of preterm PROM in breech presentation ($n=2$), abnormal bleeding from placental previa or low-lying placenta ($n=1$), uterine rupture ($n=1$), and HDP ($n=1$). Nevertheless, we believe that no specific reason was attributable to preterm delivery during pregnancy after MPA therapy. Furthermore, Arendas et al. have reported that after MPA therapy, a pregnant woman voluntarily underwent a C-section for fear of placenta accreta and to avoid the risk of uterine rupture, although neither occurred [12]. From our data, uterine rupture was more frequent in the control group than in the MPA therapy group. However, further prospective research should be performed to determine this association when patients have a vaginal delivery after MPA therapy.

In our hospital, TCR has recently been performed to evaluate the effect of MPA therapy, since it has been previously reported as useful [13]. Although TCR for endometrial cancer could spread cancer cells through the fallopian tubes into a patient's peritoneal cavity [14], according to a previous randomized controlled study, hysteroscopy for endometrial cancer did not increase the risk of the intraperitoneal transport of cancer cells [15]. When compared with D&C, TCR allows for the tumor to be removed quickly and effectively; Nevertheless, both TCR and D&C could minimize damage to the uterine muscle layer and endometrium and contribute to improved perinatal outcomes.

This study had some limitations. First, this was a retrospective study with a small sample size; however, this is the largest study on pregnancy after MPA therapy and PMS was used to evaluate obstetric outcomes. Thus, our results could be meaningful in the management of pregnant patients after

MPA therapy. Second, approximately half of the patients who received MPA therapy were delivered at other hospitals. Since we were unable to obtain their detailed information, we evaluated perinatal outcomes in women who received MPA therapy at our hospital.

In conclusion, pregnancy after MPA therapy is associated with a high risk of placenta accreta. In cases with a high frequency of D&C, placenta accreta should be considered.

Acknowledgements We would like to thank all medical staff in the obstetric units of Keio University Hospital for excellent patient care. We would like to thank Editage (www.editage.jp) for English language editing.

Author contributions MK collected the data, wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. YK and WY wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. YT, AH, JT, YT, KH, TY, SI, and DO contributed to the discussion, and reviewed and edited the manuscript. MT supervised.

Funding This study was supported by the JSPS KAKENHI (Grant No. 20K18173).

Data availability The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors report there are no competing interests to declare.

References

1. Yamagami W, Aoki D (2015) Annual report of the committee on gynecologic oncology, the japan society of obstetrics and gynecology. J Obstet Gynaecol Res 41:1861–1869
2. Gallos ID, Yap J, Rajkhowa M et al (2012) Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 207:266.e1-266.12
3. Yamagami W, Susumu N, Makabe T et al (2018) Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? J Gynecol Oncol 29:e21
4. Inoue O, Hamatani T, Susumu N et al (2016) Factors affecting pregnancy outcomes in young women treated with fertility-preserving therapy for well-differentiated endometrial cancer or atypical endometrial hyperplasia. Reprod Biol Endocrinol 14:2
5. Ota Y, Watanabe H, Fukasawa I et al (1999) Placenta accreta/increta. Review of 10 cases and a case report. Arch Gynecol Obstet 263:69–72
6. Greenbaum S, Wainstock T, Dukler D et al (2017) Underlying mechanisms of retained placenta: evidence from a population based cohort study. Eur J Obstet Gynecol Reprod Biol 216:12–17
7. Baldwin HJ, Patterson JA, Nippita TA et al (2018) Antecedents of abnormally invasive placenta in primiparous women: risk associated with gynecologic procedures. Obstet Gynecol 131:227–233
8. Beuker JM, Erwich JJ, Khong TY (2005) Is endomyometrial injury during termination of pregnancy or curettage following miscarriage the precursor to placenta accreta? J Clin Pathol 58:273–275
9. Tamauchi S, Kajiyama H, Utsumi F et al (2018) Efficacy of medroxyprogesterone acetate treatment and retreatment for atypical endometrial hyperplasia and endometrial cancer. J Obstet Gynaecol Res 44:151–156
10. Vaugon M, Peigné M, Phelippeau J et al (2021) IVF impact on the risk of recurrence of endometrial adenocarcinoma after fertility-sparing management. Reprod Biomed Online 43:495–502
11. Park JY, Seong SJ, Kim TJ et al (2013) Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol 121:136–142
12. Arendas K, Aldossary M, Cipolla A et al (2015) Hysteroscopic resection in the management of early-stage endometrial cancer: report of 2 cases and review of the literature. J Minim Invasive Gynecol 22:34–39
13. Yang HC, Liu JC, Liu FS (2019) Fertility-preserving treatment of stage IA, well-differentiated endometrial carcinoma in young women with hysteroscopic resection and high-dose progesterone therapy. Taiwan J Obstet Gynecol 58:90–93
14. Polyzos NP, Mauri D, Tsioras S et al (2010) Intraperitoneal dissemination of endometrial cancer cell after hysteroscopy. Int J Gynecol Cancer 20:261–267
15. Cicinelli E, Tinelli R, Colafiglio G et al (2010) Risk of long-term pelvic recurrences after fluid minihysteroscopy in women with endometrial carcinoma. Menopause 17:511–515