

## Fertility-sparing Management of Grade 2 and 3 Endometrial Adenocarcinomas

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**Abstract.** We report four cases of grade 2 and 3 endometrial adenocarcinomas managed conservatively in order to preserve fertility. In the literature, seven other cases have been reported. We discuss the management of these cases and compared the carcinologic and fertility outcomes with fertility-sparing management of grade 1 endometrial adenocarcinoma.

Fertility-sparing management has been used and reported for many years in young women with grade 1 endometrial adenocarcinoma (1), but it is unclear whether it can be safely used in cases of grades 2 and 3 diseases. We report three grade 2 and one grade 3 endometrial adenocarcinomas managed conservatively. The histological slides were reviewed by a panel of five expert pathologists (Pathgyn) using uniform pathological criteria. All the patients were nulligravid and requested preservation of fertility after full information of the risks they were running. In all the patients, magnetic resonance imaging (MRI) showed a tumor limited to the endometrium.

### Case Reports

*Case 1.* A 41-year-old woman underwent hysteroscopy for infertility. Hysteroscopy showed a papillary polyp and curettage revealed a grade 2 endometrioid carcinoma. Exploratory laparoscopy did not show extrauterine disease.

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The patient was given progestin (norethisterone 20 mg per day) for 3 months, after which endometrial biopsy showed complete remission. The patient was invited to conceive without delay. Three months after remission, hysteroscopy with endometrial biopsy showed a recurrence (grade 1 endometrial adenocarcinoma). One year after the diagnosis of endometrial cancer, the patient still refused hysterectomy.

*Case 2.* A 32 year-old woman underwent curettage because of metrorrhagia and endometrial hypertrophy. Pathological examination revealed a grade 2 endometrioid carcinoma. Exploratory laparoscopy did not show extrauterine disease. The patient was given progestin (megestrol acetate 160 mg per day) for six months, after which endometrial biopsy showed complete remission. Six months later, spontaneous twin pregnancy was obtained and the patient delivered two healthy children.

*Case 3.* A 35-year-old woman underwent hysteroscopy for infertility. Her medical history was marked by arterial hypertension, polycystic ovary syndrome and morbid obesity. Curettage revealed a grade 2 endometrioid carcinoma. The patient was given progestin (nomegestrol acetate 5 mg per day) for five months, after which endometrial biopsy showed complete remission. The patient was invited to conceive without delay. Diagnostic hysteroscopy and endometrial biopsy were performed every 6 months. Three years after remission, grade 1 endometrial adenocarcinoma was diagnosed and hysterectomy was performed. Pathologic examination showed a stage IA grade 1 endometrial adenocarcinoma.

*Case 4.* As part of an investigation of infertility, a 42-year-old woman underwent hysteroscopy, which revealed a suspicious endometrial lesion. A grade 3 endometrioid carcinoma was confirmed by biopsy. Exploratory laparoscopy

Table I. Literature review on fertility-sparing management of grade 2 and 3 endometrioid adenocarcinomas.

Reference	Grade	Medical therapy	Response, months	Relapse, months	Hysterectomy	Pregnancy	Status, follow-up (months)
Kaku <i>et al.</i> (3)							
Case 1	2	MPA	CR, 4	No	No	NFTD	NED, 19
Case 2	2	MPA	No	-	Yes	No	NED, 22
Gotlieb <i>et al.</i> (4)							
Case 1	2	MPA	CR, 3	Yes, 40	Yes	NFTD	NED, 94
Case 2	3	MPA	CR, 5	No	NR	No	NED, 18
Case 3	3	Megestrol	CR, 3	No	NR	No	NED, 16
Imai <i>et al.</i> (5)							
Case 1	2	MPA	CR	Yes, 7	No	No	Recurrence, 7
Case 2	2	MPA	No	-	Yes	No	NED, 47
Sardi <i>et al.</i> (6)	2	MPA	No	-	Yes	No	NED, 20
Zuckerman <i>et al.</i> (7)	2	MPA	CR, 2	No	Yes	Twin pregnancy by IVF	NED
Present cases							
Case 1	2	Norethisterone	CR, 3	Yes, 6	No	No	EA, G1, 6
Case 2	2	Megestrol	CR, 6	No	No	NFTD	NED, 24
Case 3	2	Nomegestrol	CR, 5	Yes, 36	Yes, EA, G1	No	NED, 60
Case 4	3	Triptorelin and Norethisterone	No	-	Yes, EA, G3	No	NED, 23
Total	10 G2, 3 G3		CR: 9/13	Relapse: 4/9	7/13	4/13	NED: 11/13

MPA: Medroxyprogesterone acetate; CR: complete response; EA: endometrial adenocarcinoma; G: grade; NFTD: normal full-term delivery; IVF: *in vitro* fertilization; NED: no evidence of disease.

did not show extrauterine disease. The patient was given two injections of gonadotropin-releasing hormone agonist (triptorelin 11.25 mg/3 months). The second injection was given because of persistent grade 3 endometrioid carcinoma 3 months after the first injection. New endometrial biopsy showed persistent endometrioid carcinoma and the MRI showed one-third myometrial invasion. The patient underwent radical surgery and pathologic examination showed stage IA grade 3 endometrioid carcinoma.

## Discussion

Most studies suggest that conservative management is safe in patients with grade 1 adenocarcinoma limited to endometrium. Nevertheless, no prospective study of fertility-sparing management has included grade 2 and 3 adenocarcinomas. The decision to exclude grade 2 and 3 adenocarcinomas is based on a lower sensitivity of poorly differentiated adenocarcinoma when treated with progestin (2). Thigpen *et al.* showed that response rates were higher in grade 1 endometrial adenocarcinoma in comparison with grade 2 and 3 (response rates were respectively 37, 23 and 9%).

A review of the literature on fertility-sparing management of grade 2 and 3 endometrioid carcinomas (3-7) (Table I) shows an 9/13 complete response rate with an 4/9 relapse

rate (3-7). In a review of 133 patients with adenocarcinoma treated conservatively with progestin, a lasting complete response was obtained in more than 50% of cases (8). One could argue that the less satisfactory outcome of grade 2 and 3 endometrial adenocarcinomas should discourage fertility-sparing management with similar lesions. However, the accuracy of dilation and curettage in histologic grading of endometrial carcinoma is poor and we can assume that subscribing to the principle of conservative management implies acceptance of a poor characterization of the endometrial lesion. In order to limit the impact of such poor characterization, close follow-up is mandatory to diagnose progression of the disease as early as possible.

Cases of death after conservative management have been reported for grade 1 endometrial adenocarcinoma (9) and atypical hyperplasia (10) but it has never been reported for patients with grade 2 and 3 lesions. Various reasons can explain this discrepancy. It is not possible to say if all unfavorable cases concerning fertility-sparing surgery have been published and no one can prove if deaths can be attributed to a conservative approach. It is probable, however, that the frequent use of hysterectomy has permitted a safe outcome for patients with grade 2 and 3 lesions.

Finally, the pregnancy rate of 4/13 revealed in this review concerning a limited number of grade 2 and 3

adenocarcinomas should encourage further evaluation of fertility-sparing management. Considering the lower sensitivity of poorly differentiated adenocarcinoma when treated with progestin, patients should be counseled regarding the need for close follow-up and should be prepared for the possibility of hysterectomy even when reproductive desires have not been fulfilled.

### Disclosure Summary

The Authors have nothing to disclose.

### Conflict of Interest Statement

The Authors declare that there are no conflicts of interest.

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