

Original Article

Effectiveness of Megestrol for the Treatment of Patients with Atypical Endometrial Hyperplasia or Endometrial Endometrioid Adenocarcinoma (Stage IA, Well Differentiated)

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INTRODUCTION

Endometrial hyperplasia is defined as a hyperproliferation of endometrial glands and increased glands to stromal ratio.^[1] In some conditions, this hyperproliferation is considered precancerous. There are two major categories for endometrial hyperplasia: nonneoplastic and endometrioid and intraepithelial neoplasia.^[2,3] Atypical endometrial hyperplasia (AEH) is the primary cause of endometrial cancer. In most cases, endometrial hyperplasia is caused due to high estrogen secretion and a lack of sufficient progesterone.^[3,4] Other influencing factors include obesity, diabetes, and aging.^[3] Atypical hyperplasia and endometrial cancer are most prevalent near or after menopause and are only detected

ABSTRACT

Objective: We aimed to evaluate treatment responses and recurrence rate of atypical endometrial hyperplasia (AEH) and endometrial endometrioid adenocarcinoma (EA) with Stage IA Grade 1 to megestrol in Iranian patients who are candidates for medical treatments. **Methods:** In a retrospective cohort study that was conducted on 50 patients with AEH and 22 patients with EA who were referred to the oncology clinic of Imam Khomeini Hospital, Tehran, Iran, during 2006–2016, we recruited all patients with AEH or EA of Stage IA Grade 1 and their disease was diagnosed during endometrial curettage with or without hysteroscopy. Patients were initially treated with 160 mg of megestrol daily, along with aspirin up to 3 months, and then after 3–4 weeks of discharge of the drugs, patients underwent curettage with hysteroscopy. **Findings:** The patients with AEH had 31 complete responses and five progressive diseases, and the patients with EA had seven complete responses and seven progressive diseases. After treatment, 25 cases with AEH and 5 cases with EA had an intention to get pregnant, whereas eight patients with AEH and 1 case with endometrial cancer became pregnant. Recurrence occurred in the 2 cases with AEH and 2 cases with endometrial cancer which the time of recurrence in the patients with AEH was longer than in patients with endometrial cancer ($P = 0.011$). **Conclusion:** Megestrol is an effective therapeutic agent in endometrial hyperplasia or low-grade endometrial cancer patients who are willing to conserve their childbearing.

KEYWORDS: Atypical endometrial hyperplasia, endometrial endometrioid adenocarcinoma, Megestrol

in 2%–14% of women under 40.^[5] In this age group, most endometrial cancers are low grades of endometrioid cancer. Studies have indicated that these women often have a history of sex hormone dysfunction, chronic anovulation, infertility, diabetes, hypertension, obesity, or Polycystic Ovarian Disease (PCOD).^[2,6] Different lines of evidence emphasized the importance of treatments for atypical hyperplasia and reported that almost 25%

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of cases would proceed to carcinomas.^[7] Furthermore, it should also be noted that standard treatments of endometrioid cancer in Stage IA include hysterectomy plus total bilateral salpingo-oophorectomy (BSO), but younger women are eager to perform alternative surgeries to keep uterus and fertility.^[8]

There have been studies on the functions of medical treatments such as progestin, especially by using an intrauterine device (IUD) for AEH and endometrial endometrioid adenocarcinoma (EA) with Stage IA.^[9,10] Jadoul *et al.* reported 83%–94% response rate for atypical hyperplasia and 57%–75% response rate for EA with Stage IA.^[11] There might be also relapses associated with medical treatments, and patients should be followed for several months. Documents emphasize the importance of hysterectomy right after childbearing in women under medical treatments.^[11] Most studies have been performed on the medical effects of IUD devices that contain levonorgestrel, and the medical impacts of megestrol or medroxyprogesterone, which are orally administered progesterone, on AEH and EA have been less studied.^[12] The importance of treatments with megestrol is that this drug acts with lower dosages compared with medroxyprogesterone and has fewer side effects.^[13] Most women complain about spotting and irregular bleeding during medical treatments with medroxyprogesterone, and these problems are much annoying in Iranian women due to religious beliefs, and as a result, megestrol could be a better replacement.^[14] This study aimed to evaluate treatment responses and recurrence rate of AEH and EA with Stage IA to megestrol in Iranian candidates for medical treatments.

METHODS

The current study was a retrospective cohort analysis that included 50 patients with AEH and 22 patients with EA referred to the Imam Khomeini Hospital's cancer clinic archive between 2006 and 2016. The study protocol and the clearance for accessing the patients' data were approved and issued by the board of human studies of Tehran University of Medical Sciences. The disease was diagnosed in all patients during endometrial curettage with or without hysteroscopy, and the pathology was reappraised by a retrieval pathologist with experience. The inclusion criteria were age under 40, desire to preserve fertility, pathology of AEH, or endometrial EA of Stage IA Grade 1, candidates for medical treatment with megestrol. Patients were excluded from the study if we did not have access to their needed data. As is standard procedure at our hospital for all similar patients, they were all informed and fully aware of the

risks of nonresponse, disease progression during drug treatment, the need for surgical removal of the uterus during treatment due to the advancement of the AEH to endometrial cancer, or the lack of response or progression of endometrial EA of Stage IA. Hysterectomy was done due to the lack of AEH response to medical therapy after a maximum of 12 months treatment which requires curettage every 3 months to evaluate the response to treatment. Before drug therapy initiation, all patients underwent TVS and magnetic resonance imaging, and the cases with evidence of invasion to myometrium were excluded from the study. Furthermore, any malignant lesion in the uterus other than AEH or endometrial endometrioid adenocarcinoma of Stage IA Grade 1 was excluded before starting treatment.

Patients were initially treated with a daily 160 mg dose of megestrol, along with aspirin up to 3 months, and 3–4 weeks after stopping drugs, patients underwent curettage with hysteroscopy. If any of the patients were progressed, surgical removal of the uterus was performed, and in the absence of response, the dosage of the drug increased to 320 mg daily with aspirin administration and continued for up to 3 months; every 3 months, the response to treatments was evaluated with curettage under the hysteroscopic procedure.

Patients with progressive disease or patients unresponsive to medical treatment until 12 months were a candidate for hysterectomy. Patients who had complete responses and intended a quick pregnancy were referred to the infertility medical service. If the patient currently had a “tendency to delay pregnancy, she was treated with a 40 mg/day dose of megestrol and preservative treatment and also had follow-up every 6 month. Response to treatment, relapse rate, and disease progression were evaluated and recoded until 5 years by pathological examinations.

Age, hypertension, diabetes mellitus, gravidity, parity, primary complaint, history of infertility, Polycystic ovary disease (PCOD), type of histology, body mass index (BMI), duration of treatment, and patient's marital status were also evaluated and documented.

The data were analyzed using the SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp.). The quantitative data were presented as mean \pm standard deviation, and qualitative data were presented as frequencies or percentages. A significant level of $<5\%$ was considered. Parametric analyses were used to analyze the variables with normal distribution and nonparametric analyses for analysis of variables with an abnormal distribution.

RESULTS

In this study, patients were divided into two groups: fifty patients with AEH (mean aged 32.4 ± 4.8 years; mean BMI 29.9 ± 7.8 kg/m²) and 22 patients with endometrial EA (mean aged 33.4 ± 5.3 years; mean BMI 26.7 ± 4.4 kg/m²). Patients' characteristics and related medical history are summarized in Table 1.

In 3 months after treatment, in patients with AEH, 46% had no response, 20% complete response, 30% partial response, and 4% progressive disease and in endometrial cancer group, 50% had no response, 9.2% complete response, 31.8% partial response, and 9% progressive disease [Table 2].

After treatment, 25 cases with AEH and 5 cases with endometrial cancer had an intention to get pregnant, whereas 8 cases with AEH and 1 case with endometrial cancer became pregnant. The pregnancy methods in patients with AEH were *in vitro* fertilization (IVF) in 2 cases, induction ovulation with drug in 6 cases, and one patient with endometrial cancer who became pregnant with IVF. Some pregnancy complications

such as intrauterine fetal demise (1 case with AEH) and preterm labor (1 case with AEH, 1 case with EA) were observed in the patients [Table 3].

Fifteen patients with endometrial endometrium hyperplasia (4 cases under TAH + BSO and 11 cases under TAH alone) and nine patients with endometrial cancer (7 cases under TAH + BSO and 2 cases under TAH alone) were under surgery because of no complete response after 12 months of medical treatment. The pathological findings after surgery are shown in Table 4.

Recurrence occurred in the 2 cases with AEH and 2 cases with EA which the time of recurrence in the patients with AEH was longer than patients with EA ($P = 0.011$). The site of recurrence in the patients with AEH was included 1 case ovary and 1 case vaginal floor, and in patients with EA were included 1 case ovary, 1 case vaginal floor, and 1 case iliac lymph nodes [Table 5].

In patients with recurrences, the mean age in the patients with AEH was 29.7 ± 4.6 years, and in the patients with endometrial cancer, it was 35.7 ± 5.2 years. Furthermore, the mean BMI in the AEH and endometrial cancer was

Table 1: Patients' characteristics and related medical history

	Hyperplasia	Endometrial cancer
Age (years)	32.4±4.8	33.4±5.3
BMI	29.9±7.8	26.7±4.4
Gravity history		
Virgin	8 (16)	-
Gravid 1	26 (52)	8 (36.4)
Nongravid	13 (26)	13 (59.1)
Gravid 2	3 (6)	1 (4.5)
Parity history		
0	13 (26)	11 (50)
L1	15 (30)	4 (18.3)
Ab1	8 (16)	3 (13.6)
D1	3 (6)	1 (4.5)
D1AL1	1 (2)	-
D1Ab1	1 (2)	-
Ab2	1 (2)	-
L1Ab1	-	1 (4.5)
Missing	8 (16)	2 (9.1)
Marital status		
Single	8 (16)	3 (13.6)
Married	42 (84)	19 (86.4)
DM	9 (18)	3 (13.6)
HTN	6 (12)	5 (22.7)
PCOS	22 (44)	11 (50)
History of infertility	20 (40)	10 (45.5)
Family history of cancer	4 (8)	3 (13.6)

Data are presented as mean±SD or n (%). BMI=Body mass index, PCOS=Polycystic ovary syndrome, DM=Diabetes mellitus, HTN=Hypertension, SD=Standard deviation

Table 2: Duration of received treatment and clinical response in studied patients

	Hyperplasia	Endometrial cancer
3 months		
Clinical response		
Nonresponse	23 (46)	11 (50)
Complete response	10 (20)	2 (9.2)
Partial response	15 (30)	7 (31.8)
Progressive disease	2 (4)	2 (9.2)
6 months		
Clinical response		
Nonresponse	15 (39.5)	9 (50)
Complete response	6 (15.8)	2 (11.1)
Partial response	16 (42.1)	5 (27.8)
Progressive disease	1 (2.6)	2 (11.1)
9 months		
Clinical response		
Nonresponse	8 (25.8)	6 (42.9)
Complete response	6 (19.3)	2 (14.3)
Partial response	16 (51.6)	4 (28.6)
Progressive disease	1 (3.2)	2 (14.3)
12 months		
Clinical response		
Nonresponse	8 (33.3)	5 (50)
Complete response	9 (37.5)	1 (10)
Partial response	6 (25)	3 (30)
Progressive disease	1 (4.2)	1 (10)
Drug dose (mg)		
160	11 (22)	4 (18.2)
320	39 (78)	18 (81.8)

Data are presented as n (%)

38.8 ± 1.9 and 31.2 ± 4.2 kg/m², respectively. The frequency of gravity and parity in AEH was 50% G1 and 50% NG and 100% parity 0 and in the endometrial cancer group, there were 50% G1 and 50% NG and 50% parity 0, 50% L1. 100% of AEH and endometrial cancer groups were married. In the endometrial atypical hyperplasia group, 100% had DM, 50% had HTN, 100% had PCOS, 50% had a history of infertility, and 66.7 had a family history of cancer, and in the endometrial cancer group, 100% had DM, 50% had HTN, 100% PCOS. Surgery was recommended for all patients with recurrences in AEH and endometrial cancer. The pathological findings of other characteristics of patients with recurrence are summarized in Table 6.

DISCUSSION

Here in this study, we evaluated 50 patients with AEH and 22 patients in Stage IA and well-differentiated EA and assessed their response to megestrol. We indicated that most of the patients with hyperplasia responded entirely or partially to megestrol, although some progressive cases were reported in this group. Furthermore, our results suggested that the pregnancy

rate was higher in patients with hyperplasia than with cancer, and the most commonly administered pregnancy method was assisted reproductive technology (ART). On the other hand, in those patients who required a surgical procedure, TAH + BSO was the standard method in patients with cancer, and TAH was most common in patients with hyperplasia. In a study by Simpson *et al.*, 44 patients with complex atypical hyperplasia and Grade 1 endometrial cancer were evaluated and treated with oral progestin. They reported that oral progestin is an effective and temporizing fertility-sparing treatment that increases childbirth in patients. They also recommended that reevaluation be performed for nonresponsive patients and that also hysterectomy must be performed after childbearing.^[15] These data are in line with our study. We also indicated that megestrol could be an effective conservative method in patients with endometrial atypical hyperplasia or Stage IA of well-differentiated endometrioid endometrial adenocarcinoma who tend to be pregnant. A meta-analysis study by Gallos *et al.* in 2012 reported that conservative treatment of patients with endometrial hyperplasia or endometrial cancer is feasible with oral progesterone.^[16] In another study by Shan *et al.* performed in 2014, they had a survey on 16 patients with AEH and at least one criterion of metabolic syndrome. Patients were treated with megestrol acetate and metformin and concluded that metformin plus megestrol acetate could be a potential alternative therapy in patients.^[17] These studies emphasize the therapeutic effects of oral progesterone in patients with endometrial hyperplasia and are along with our results.

Gunderson *et al.* declared that hormonal therapies might bring better results in patients with endometrial hyperplasia than those with Grade 1 endometrial carcinoma.^[18] They had performed a systematic review

Table 3: Post-treatment pregnancy details in studied patients

	Hyperplasia	Endometrial cancer
Tend to be pregnant	25 (80.6)	5 (71.4)
Pregnant	8 (32)	1 (20)
Pregnancy method		
IVF	2 (25)	1 (100)
Induction ovulation	6 (75)	-
Pregnancy complication		
IUFD	1 (12.5)	-
Preterm	1 (12.5)	1 (100)

Data are *n* (%). IVF=*In vitro* fertilization, IUFD=Intrauterine fetal death

Table 4: Number and type of surgery and pathologic characteristics in studied patients

	Hyperplasia	Endometrial cancer	<i>P</i>
Surgery	15 (30)	9 (40.9)	
Type of surgery			
TAH + BSO	4 (26.7)	7 (77.8)	0.006
TAH	11 (73.3)	2 (22.2)	
Pathologic characteristics			
Normal	1 (6.6)	0	0.18
Grade I adenocarcinoma without spread in the myometrium	3 (20)	2 (22.2)	
Grade I adenocarcinoma with <50% spread in myometrium	2 (13.6)	2 (22.2)	
Grade I adenocarcinoma with a spread in ≥50% of the myometrium	1 (6.6)	2 (22.2)	
Endometrial atypical hyperplasia	6 (40)	0	
Grade II adenocarcinoma with a spread in <50% of the myometrium	1 (6.6)	1 (11.1)	
Grade II adenocarcinoma with a spread in >50% of the myometrium	1 (6.6)	1 (11.1)	
Grade III adenocarcinoma with a spread in <50% of myometrium	0	1 (11.1)	

Data are presented as *n* (%). TAH=Total abdominal hysterectomy, BSO=Bilateral salpingo-oophorectomy

in 2012 and reported that patients with hyperplasia have a better chance of response to megestrol than patients with endometrial cancer. They also reported no significant differences between patients with endometrial hyperplasia and those with Grade 1 endometrial carcinoma regarding reproductive outcomes. Oral progesterone is considered an effective therapy in patients with endometrial hyperplasia as well as endometrial cancer. Shan *et al.* also performed a

study on 26 patients with endometrial hyperplasia and cancer and reported that fertility-sparing treatment with megestrol acetate following entirely hysteroscopic curettage is an effective method and increases the chances of fertility.^[19] This study is also in line with our research, which showed the importance and efficacy of oral progesterone in endometrial hyperplasia and cancer. All these studies emphasize the roles of megestrol and conservative therapies in patients with endometrial hyperplasia and cancer. There are also other therapeutic methods evolved in curing endometrial hyperplasia. As Gallos *et al.* reported, oral progesterone has a lower disease regression rate than the levonorgestrel-releasing intrauterine system.^[20] These results emphasize that further studies on a more extensive study population might be required to evaluate these therapeutic methods. In another study by Eftekhar *et al.* in 2014, the efficacy of megestrol in treatments of early endometrial cancer is proven. They also reported that pregnancy occurred in 27.78% of patients, which is somehow in line with our result. In those patients with progressive disease, surgical methods, including TAH + BSO, are required.^[21]

Table 5: Recurrence characteristics in studied patients

	Hyperplasia	Endometrial cancer	P
Recurrence	2 (6.4)	2 (28.5)	0.190*
Time to recurrence (months)	48	21.7±4.9	0.011#
Cite of recurrence			
Ovary	1 (50)	1 (50)	
Vaginal floor	1 (50)	-	
Iliac lymph nodes	-	1 (50)	

P values calculated by *Chi-square test and #One sample t-test (in hyperplasia group, time to recurrence was available only for one patient and in endometrial cancer group for three patients was available). Data are mean±SD or n (%). SD=Standard deviation

Table 6: Patients characteristics with recurrence

	Hyperplasia	Endometrial cancer
Age (years)	29.7±4.6	35.7±5.2
BMI	38.8±1.9	T
Gravidity		
G1	1 (50)	1 (50)
NG	1 (50)	1 (50)
Parity		
0	2 (100)	1 (50)
L1	0	1 (50)
Marital status		
Virgin	0	0
Married	2 (100)	2 (100)
DM	2 (100)	2 (100)
HTN	1 (50)	1 (50)
PCOS	2 (100)	2 (100)
History of infertility	1 (50)	2 (100)
Family history of cancer	1 (50)	0
12 months drug treatment	2 (100)	2 (100)
Surgery after recurrence	2 (100)	2 (100)
Type of surgery		
TAH + BSO	1 (50)	2 (100)
TAH	1 (50)	0
Pathologic characteristics		
Grade I adenocarcinoma with a spread in <50% of the myometrium	0	0
Grade I adenocarcinoma with a spread in ≥50% of the myometrium	1 (50)	0
Grade II adenocarcinoma with a spread in <50% of the myometrium	1 (50)	1 (50)
Grade II adenocarcinoma with a spread in ≥50% of the myometrium	0	1 (50)
Grade III adenocarcinoma with a spread in <50% of the myometrium	0	0

Data are mean±SD or n (%). BMI=Body mass index, PCOS=Polycystic ovary syndrome, DM=Diabetes mellitus, HTN=Hypertension, SD=Standard deviation, TAH=Total abdominal hysterectomy, BSO=Bilateral salpingo-oophorectomy

Taken together, we indicated that megestrol as oral progesterone is an effective therapeutic method in patients with AEH or in Stage IA – Grade 1 endometrioid endometrial adenocarcinoma who are willing to conserve their childbearing. These patients, especially patients with hyperplasia, respond well to megestrol therapies. Reproductive methods such as ART are much helpful for those patients who tend to be pregnant after their successful medical treatment, and in those patients who do not respond to megestrol, surgical treatments such as TAH or TAH + BSO are required.

Our study shows that Megestrol is an effective therapeutic agent in the treatment of endometrial hyperplasia or low-grade endometrial cancer patients who are willing to conserve their childbearing.

AUTHORS' CONTRIBUTION

All authors contributed in the development of the idea, concept, data gathering and analysis of the data and contributed to the manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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