Progestin Treatment of Atypical Hyperplasia and Well-differentiated Adenocarcinoma of the Endometrium to Preserve Fertility

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Abstract. *Aim: To evaluate the outcome of a cohort of young women treated with progestin for fertility-sparing management of endometrial atypical hyperplasia (AH) and endometrial carcinoma (EC). This retrospective multicentre cohort study included women under the age of 40 years treated conservatively for AH and EC to preserve fertility using progestin for at least 3 months. Four inclusion criteria were defined: (i) the presence of AH or grade 1 EC confirmed by two pathologists (including a reference pathologist); (ii) the use of conservative management for fertility sparing; (iii) adequate radiological examination before conservative management; and (iv) a minimal follow-up time of one year. Results: Twenty-two patients fulfilled the inclusion criteria (8 had EC, and 14 had AH). After progestin treatment, 17 patients responded. Among the 17 patients who experienced remission, three also experienced disease relapse. One patient initially diagnosed with AH experienced progression of her disease to stage IIIA EC. Ten pregnancies were achieved in eight patients. Conclusion: Fertility-sparing management using progestin offers the opportunity to fulfil maternal desires in young patients diagnosed with AH and EC. However, progression of the disease is possible and close follow-up is needed.*

Endometrial carcinoma (EC) and atypical hyperplasia (AH) are typically diseases of postmenopausal women. However, approximately 5% of patients are diagnosed with such diseases before the age of 40 years (1). AH is the least common type of hyperplasia but is the most likely to progress to EC (2). Both histological types share the same risk factors and are related to excess of oestrogens relative to progesterone (3).

Forty years ago, the principle of uterine sparing for the purpose of future fertility was reported in the literature (4, 5). Currently, delaying childbearing to a later age has led to an increasing number of women with cancer who wish to become pregnant. Such conservative therapy has led to successful pregnancies in a large number of patients.

Oral progestin remains the most evaluated therapy. Other therapies that have been evaluated in a limited number of cases include gonadotropin-releasing hormone (GnRH) agonist (6), intrauterine devices containing progestogen (7) or a combination of both (8). Other widely used therapies include 17-hydroxyprogesterones, such as medroxyprogesterone acetate (MPA), megestrol acetate (MA) and chlormadinone acetate (CA) (9, 10), whereas fourth-generation progestins, such as nomegestrol acetate (NA) and lynestrenol, have not been evaluated for this indication. Nomegestrol, a norprogesterone derivate, has been proven to have a strong antiandrogenic action without estrogenic activity (11, 12). Lynestrenol has been suggested to be more efficient than MPA for the management of endometrial hyperplasia (13).

Even if spontaneous pregnancies can occur after remission, Gurgan *et al*. have encouraged the use of assisted reproductive technologies (ART) because they permit rapid reproductive success with favourable recurrence and survival rates (14).

Conservative management has been proposed for EC and AH, but severe progression has been reported for both (15-19).

The objective of this study was to report the oncologic and reproductive outcomes of patients with AH and well-differentiated EC who were managed conservatively using progestin.

Patients and Methods

Patients. We conducted a retrospective multicentre analysis of patients with AH and EC who were managed conservatively between 2001 and 2010 in ten French gynaecological units. For each patient, data on the clinical characteristics, surgical management and patient outcomes were extracted from the medical record.

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Patients were included if they had been managed conservatively for AH and EC before the age of 40 and if they met the following four inclusion criteria: i. The diagnosis of grade 1 EC or AH was confirmed independently by two pathologists. The histological slides of the endometrial tumour were reviewed by the same reference pathologist (FW). Patients with grade 2 or 3 EC who were treated conservatively were excluded and reported in another article (20). ii. The patient had a strong desire to preserve fertility. We excluded all cases that used conservative management due to any concern other than fertility sparing (*e.g.* medical contraindication to surgery). iii. An adequate radiological examination was conducted prior to conservative management. This was defined as at least an ultrasound examination for AH and at least magnetic resonance imaging (MRI) for EC. Cases of EC invading the myometrium as shown on MRI were excluded from the study. iv. Each patient was followed-up for a minimum period of one year.

Patients who met the criteria were counseled extensively regarding the risk of recurrence or progression if they chose hormone therapy. All desired to preserve pregnancy and gave informed consent for the treatment.

Hormone therapy. The patients who met the inclusion criteria were treated with progestin for at least three months. The following three types of progestin were used: NA, 17-hydroxyprogesterone derivate (MPA, MA or CA) and lynestrenol. Because a higher incidence of synchronous ovarian cancer in young patients has been reported (21, 22), a diagnostic laparoscopy was performed prior to progestin treatment in the last 14 patients. In no case did laparoscopic findings modify disease staging.

Follow-up. Response was assessed using the pathological specimens obtained at curettage or endometrial biopsy after 3-6 months of progestin therapy. Lesions were defined as having regressed, persisted, or progressed based on a comparison with the last available specimen. Complete remission was indicated if the last endometrial sample or hysterectomy specimen showed normal endometrium or hyperplasia without atypia. Persistence was indicated if the last biopsy showed AH or EC when the entry biopsy showed AH or grade 1 EC. Progression was indicated if the last tissue specimen showed EC for patients diagnosed with AH or if the last tissue sample showed grade 2 or 3 EC for patients diagnosed with EC on entry. Recurrence was indicated if a lesion that had initially regressed following treatment reappeared. Lasting remission was indicated if regression had been achieved, and no recurrence occurred. Because all patients had at least one year of follow-up, lasting remission lasted at least one year.

For patients showing no response to progestin therapy, the plan was to propose total hysterectomy with or without bilateral salpingo-oophorectomy (BSO). If the patient refused, another treatment based on GnRH agonist was used (6).

After the documentation of complete remission, women were followed-up every 3-6 months with diagnostic hysteroscopy and endometrial biopsy. Patients were encouraged to conceive spontaneously. ART was attempted after complete remission. The decision to undergo ART [ovulation induction, *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI)] was based on the couple's fertility parameters. Women with anovulation or polycystic ovary syndrome (PCOS) were candidates for ovulation induction using clomiphene acetate or IVF, and couples with spermatic disorders were more likely to undergo ICSI. Women who failed in their attempt to conceive or who successfully completed childbearing were encouraged to undergo definitive surgery.

Statistical analysis. The Pearson χ^2 test and two-sided *t*-test were employed for statistical analysis. Significance was held at the standard value of $p<0.05$.

Approval for this research was obtained from the French Ethics Committee of the College National des Gynécologues Obstétriciens Français (Institutional Review Board number: 2010-019).

Results

Twenty-two patients were included in the study; 14 had AH, and 8 had EC.

Patient, pathological and treatment characteristics (Table I). The patients' ages ranged from 28 to 40 years. None of the patients had a family history consistent with hereditary non-polyposis colon cancer (HNPCC). Most patients were nulliparous (86%). The diagnosis of endometrial lesions was performed during investigations of infertility in 16 cases (73%) and irregular bleeding in the remaining 6 cases (27%). Metrorrhagia was associated with infertility in five cases. All cases of EC were staged IA (1988 FIGO classification) and of the endometrioid type.

After treatment with progestin for 3 to 6 months, 17 patients (77%) responded as evidenced by the absence of any abnormal histology on follow-up endometrial biopsy. Among them, three patients developed a local recurrence diagnosed by routine endometrial sampling during follow-up.

For two patients (patients 5 and 21), a secondary treatment based on GnRH agonist (triptorelin) was administered due to the presence of a persistent endometrial lesion after initial progestin therapy. Both experienced remission. Patient 5 achieved spontaneous pregnancy and underwent hysterectomy after delivery (40 months after initial diagnosis of EC). Patient 21 developed a local recurrence 43 months after the initial diagnosis and also underwent hysterectomy. The other three patients with persistent (patients 6 and 9) or progressive (patient 2) disease on routine endometrial sampling underwent hysterectomy.

When comparing oncologic outcomes of patients who underwent ART with those who tried to conceive spontaneously, 2/7 and 2/15 experienced recurrence ($p=0.338$), respectively.

No patient had severe complications or adverse effects during treatment; none experienced thromboembolism, liver dysfunctions, or weight gain.

Follow-up, oncologic and reproductive outcomes (Table II). Median and mean follow-up periods lasted 39 (range: 14-86) months and 40.4 (±23.4) months, respectively.

Eight patients achieved ten pregnancies and delivered eight full-term healthy infants. One patient (patient 10)

Table I. *Clinical characteristics of patients who received progestin for endometrial atypical hyperplasia or carcinoma.*

Patient no.	Histology	Age (years)	Personal history	Gestation parity	Progestin Therapy		Response (months)	Recurrence (months)	Lasting remission
					Treatment, dosage (mg/d)	Duration (months)			
1	EC	34	Infertility	G3P0	Lynestrenol, 15	6	CR (6)	No	Yes
2	EC	36	Bleeding	G1P0	MA, 160	3	PD	-	No
3	EC	35	Infertility	G1P0	MA, 160	3	CR (3)	No	Yes
4	EC	38	Bleeding	G3P1	MPA, 10	3	CR (3)	Yes (12)	No
5	EC	37	Infertility+ bleeding	G0P0	MPA, 10	3	SD	-	No
6	EC	28	Bleeding	G0P0	NA, 5	6	SD	-	No
7	EC	35	Infertility	G0P0	NA, 5	3	CR (3)	Yes (34)	No
8	EC	32	Bleeding	G0P0	NA, 5	3	CR (3)	No	Yes
9	AH	35	Bleeding	G0P0	CA, 10	3	SD	-	No
10	AH	35	Infertility	G0P0	CA, 10	3	CR (3)	No	Yes
11	AH	32	Infertility	G8P2	CA, 10	3	CR (4)	No	Yes
12	AH	38	Infertility	G3P0	Lynestrenol, 15	6	CR (6)	Yes (12)	No
13	AH	40	Infertility+ bleeding	G1P0	Lynestrenol, 15	6	CR (6)	No	Yes
14	AH	34	Infertility	G0P0	MA, 160	3	CR (3)	No	Yes
15	AH	39	Bleeding	G0P0	MA, 160	6	CR (6)	No	Yes
16	AH	35	Infertility	G0P0	MA, 160	6	CR (6)	No	Yes
17	AH	36	Infertility+ bleeding	G0P0	MPA, 10	3	CR (3)	No	Yes
18	AH	38	Infertility	G0P0	MPA, 10	6	CR (4)	No	Yes
19	AH	30	Infertility+ bleeding	G0P0	NA, 5	3	CR (3)	No	Yes
20	AH	29	Infertility	G0P0	NA, 5	6	CR (3)	No	Yes
21	AH	28	Infertility	G0P0	NA, 5	3	SD	-	No
22	AH	34	Infertility	G16P2	NA, 5	6	CR (6)	No	Yes

EC: Endometrial carcinoma; AH: endometrial atypical hyperplasia; MA: megestrol actetate; MPA: medroxyprogesterone acetate; NA: nomegestrol acetate; CA: chlormadinone acetate; CR: complete remission; PD: progression disease; SD: stable disease.

conceived but had a first trimester loss and was pregnant at the time this report was prepared. Median and mean time between diagnosis and the first pregnancy were 11.5 (range: 8-16) months and 12.0 (±2.6) months, respectively.

Six pregnancies were spontaneous, and the mean time between diagnosis and the first pregnancy was 12.6 (±2.1) months. The four other pregnancies resulted from ART and occurred after a mean time of 11.0 (±3.6) months. Seven patients underwent ART attempts consisting of IVF patients 11, 16, 21 and 22), ICSI (patients 1 and 10) and ovulation induction (patient 7). Out of these, three patients achieved four pregnancies by ICSI (patient 10) or IVF-ET (patients 16 and 22). Patients 1, 7, 11 and 21 did not achieve pregnancy.

Finally, nine hysterectomies were performed. Patients 2, 4, 6, 7, 9, 12 and 21 underwent hysterectomy due to progressive, persistent or recurrent disease. In all but one case, pathological examination of the surgical specimens showed an EC limited to the uterine corpus. The exception was patient 12, who underwent total abdominal hysterectomy with BSO due to recurrent disease as evidenced by the diagnosis of grade 2 EC on the follow-up endometrial biopsy, 12 months after the initial diagnosis of AH. Because of the presence of a suspicious ovarian cyst on the ultrasound examination prior to surgery, the decision was made to perform a hysterectomy and BSO with extemporaneous examination of the surgical specimens. A grade 2 endometrioid adenocarcinoma with extension to the ovary was diagnosed. Consequently, pelvic and paraaortic lymphadenectomy was performed. Final pathological examination confirmed a grade 2 EC with extension to the ovary (stage IIIA). The patient received adjuvant chemotherapy (carboplatin and paclitaxel for six cycles) and was alive without evidence of disease 32 months after the initial diagnosis of AH. In two cases (patients 5 and 22), a hysterectomy was performed after term delivery, and no residual disease was found on pathological examination.

Comparison between AH and EC for oncologic and reproductive outcomes (Table III). Complete remission rates were 5/8 and 12/14, and recurrence rates were 2/5 and 1/12 in patients with EC and AH after progestin therapy, respectively. Consequently, the lasting remission (at least one year) rate was superior in patients with AH (11/14) when compared with patients with EC (3/8), but the difference did not reach statistical significance (p=0.0541).

Similarly, the rate of ART attempts and pregnancy were higher in patients with AH when compared with patients

Table II. *Follow-up, oncological and reproductive outcomes of patients who received progestin for endometrial atypical hyperplasia or carcinoma.*

			Pregnancy			Hysterectomy			
Patient no.	PCOS or dysovulation	ART attempt	Origin	Outcome	Delay (months)	Method	Delay (months)	Stage	Follow-up (months)
1	No	ICSI	-	-	-	No	-	-	NED (84)
2	No	No	-	-	-	TAH	6	IB	NED (67)
3	No	No	-	-	-	No	-	-	NED (86)
4	No	No	-	-	-	TAH	12	IB	NED (19)
5	No	No	Spontaneous	NFTD	13	TLH	40	0	NED (44)
6	No	No	-	-	-	TAH	9	IA	NED (17)
7	Yes	OI	-	-	-	TAH+BSO	38	IB	NED (40)
8	No	No	Spontaneous (2)	NFTD (2)	16, 32	No	-	-	NED (45)
9	Yes	No	-	-	-	TLH	9	IA	NED (14)
10	No	ICSI	Assisted (2)	SA, ongoing	8, 13	No	-	-	NED (15)
11	Yes	IVF	-	-	-	No	-	-	NED (17)
12	No	No	-	-	-	TAH+BSO+PL	12	IIIA	NED (32)
13	No	No	-	-	-	No	-	-	NED (61)
14	No	No	Spontaneous	NFTD	11	No	-	-	NED (38)
15	No	No	-	-	-	No	-	-	NED (18)
16	No	IVF	Assisted	NFTD	15	No	-	-	NED (46)
17	No	No	Spontaneous	NFTD	11	No	-	-	NED (22)
18	No	No	-	-	-	No	-	-	NED (20)
19	Yes	No	Spontaneous	NFTD	12	No	-	-	NED (30)
20	No	No	-	-	-	No	-	-	NED (42)
21	Yes	IVF	-	-	-	TLH	42	IA	NED (84)
22	No	IVF	Assisted	NFTD	10	TLH	34	0	NED (48)

PCOS: Polycystic ovary syndrome; OI: ovulation induction; ICSI: intracytoplasmic sperm injection; IVF: *in vitro* fertilisation; NED: no evidence of disease; OAT: oligoasthenoteratospermia; NFTD: normal full term delivery; SA: spontaneous abortion; TAH: total abdominal hysterectomy; TLH: total laparoscopic hysterectomy; BSO: bilateral salpingo-oophorectomy; PL: pelvic lymphadenectomy.

with EC. Hysterectomy was more frequently performed in patients with EC when compared with patients with AH, but none of the differences reached statistical significance.

The length of follow-up was comparable between patients with AH and EC (35 and 50 months, respectively; p=0.1391).

Discussion

We report a series of patients with EC and AH who were treated conservatively to preserve fertility. Our results suggest that this strategy is reasonable when conducted with close follow-up. All patients included in this study were free of disease after a mean period of over three years, and more than one-third of the patients treated with progestin achieved pregnancy.

Standardized protocols for the use of progestin have recently been developed, but no randomised or observational studies have been conducted to compare different protocols for fertility-sparing management of EC and AH. Consequently, numerous unanswered questions remain.

The incidence of AH and EC detected on routine infertility investigations in young women has been estimated in a sample of the Japanese population (23). Rates were 0.03% for AH and 0.02% for EC, which is five to ten times higher than the overall incidence in women of the same age. In the present study, 73% of the women treated with conservative management for EC or AH reported infertility. Patients affected with AH or EC have various causes of infertility. Firstly, risk factors of EC and AH, particularly dysovulation, PCOS and obesity, are known to reduce fertility. Secondly, the endometrial process related to EC or AH might impair egg implantation, as polyps are accused of (24); and before showing atypical or adenocarcinomatous characteristics, such lesions were most likely polyps. In the literature, several articles report on successful management of infertile women using progestin (1-4) and at least one focused on fertility-sparing management of AH and EC in infertile women (25). In this study, involving eight patients, it is suggested that IVF treatment of infertile women conservatively treated for well-differentiated EC is highly successful.

More than 50 studies or case reports have described oncologic and reproductive outcomes after fertility-sparing management of AH or EC. However, only a limited number incorporated a large sample size (26-28). Hahn *et al*. reported

Table III. *Comparison between atypical hyperplasia and endometrial carcinoma for oncological and reproductive outcomes after progestin therapy.*

	Cases	CR (%)	Time to remission (months)	Recurrence (%)	Lasting remission (%)	ART attempt (%)	Pregnant women (%)	Time to pregnancy (months)	Total pregnancies	Spontaneous pregnancies	Pregnancies by ART	Hysterectomy (%)
EC	8	5 (62)	3.6	2/5 (40)	3/8 (37)	2 (25)	2 (25)	14.5	3	3	0	5 (62)
AH	14	12 (86)	4.4	1/12 (8)	11/14 (79)	5 (36)	6 (43)	11.2	7	3	4	4 (29)
p		0.2113	0.2960	0.1186	0.0542	0.2326	0.4023	0.1243			0.2059	0.1195
Total	22	17 (77)	4.2	3/17 (18)	14/22 (64)	7 (32)	8 (36)	12.0	10	6	4	9 (41)

CR: Complete remission; ART: assisted reproductive technologies.

encouraging results concerning the efficacy of conservative treatment with progestin and pregnancy outcomes in 35 women with early-stage EC. However, among the 22 patients (63%) who obtained complete remission, only 12 attempted to conceive; 8 of the 10 pregnancies resulted in live births (26). In their experience, extension outside the uterus never occurred. A study by Kaku *et al*. included 30 cases (12 cases of EC and 18 cases of AH) after a central pathological review; 24 (80%) showed an initial response to MPA. Unlike our report, MPA was the only therapy employed in the study of Kaku *et al*., but the dosages used were particularly variable (from 100 to 800 mg/day). Among the 12 cases of EC and the 18 cases of AH, two and five patients became pregnant, respectively. Unfortunately, two of these patients had grade 2 adenocarcinomas, which are known to respond less frequently to progestin than grade 1 carcinomas (29). Kaku *et al*. reported on one patient initially diagnosed with grade 1 EC, who underwent serious extrauterine recurrence in the left obturator lymph node (27). In a study by Randall and Kurman, among 17 patients with AH and 12 patients with EC who were treated with progestin, 25 attempted to become pregnant and five delivered healthy, full-term infants. Different progestin, dosages and duration were used. Only one case of AH and three lesions of EC persisted on the hysterectomy specimens, which were always confined to the uterus. Ushijima *et al*. conducted a prospective multicentre study to assess the efficacy of fertility-sparing treatment using MPA. Remission was found in 55% of EC cases and 82% of AH cases. During the 3-year follow-up period, 12 pregnancies were achieved. Lesions in the ovary were identified in two out of the 19 patients who underwent hysterectomy (30).

Interestingly, in our study, a secondary treatment (triptorelin) was given to two patients due to persistent endometrial lesions following the initial management. GnRH agonists have been used to treat advanced or recurrent EC (31). By substituting progestin with triptorelin, we obtained complete remission in both cases. Specific high-affinity receptors for GnRH agonists have been demonstrated in normal and carcinomatous endometrium, providing a rationale for a direct antitumor effect (32). In patients with AH and EC who want to preserve their uterus despite a poor response to progestin, this strategy appears particularly interesting.

Like others (9, 27, 28, 30, 33), we observed a trend towards a better oncological outcome in patients with AH compared with patients with EC. Such an assertion seems logical because response to progestin therapy is more frequent among patients with well-differentiated histology, and AH is precancerous rather than cancerous (29). Nevertheless, in our experience, the only distant metastasis of the endometrial lesion occurred in a patient diagnosed with AH at the beginning of treatment. Underestimation of the preoperative pathological examination is unlikely because at least two pathologists (including a reference pathologist) examined all specimens. Other cases of progression of conservatively managed AH have already been reported (15-18). Consequently, we believe that EC and AH both require close follow-up to diagnose progression of the disease as early as possible and should not be distinguished for the follow-up management. However, such a strategy has two main weaknesses: (i) progression of the endometrial lesion may not be detectable early enough, and (ii) the patient may not accept repeated and regular radiological and/or clinical examinations over a long treatment duration.

To limit these risks, several authors have proposed that patients undergo ART once in remission to achieve a rapid pregnancy (14). Attempting natural conception following remission has several disadvantages: (i) the delay of several months to achieve spontaneous pregnancy; (ii) the anxiety arising from the risk of recurrence; (iii) an increased risk of loss to follow-up and (iv) the delay of hysterectomy, if decided, until childbearing is complete. Due to these drawbacks, IVF-ET, ICSI and ovulation induction have been suggested and attempted with successful outcomes (14, 34). Although the impact of exogenous oestrogen on the endometrium remains unclear, no increase in the recurrence rate has been shown in patients who underwent ART after fertility-sparing management. In our series, the recurrence rate was twice as high in patients who underwent ART, but the difference was not statistically significant. Until more scientific evidence is available, mild protocols (*i.e*. with a shorter duration of ovarian

stimulation, a lower peak oestradiol level and a minimum number of cycles) should be preferred

In conclusion, when fertility-sparing management of AH and EC is considered, patients should be counseled about the realistic chances of pregnancy and about the risks. Information for these patients is particularly important because close follow-up is mandatory in order to detect early recurrence or persistent disease. The results of the present study demonstrate that fertility-sparing management of AH and EC with progestin alone may be successful as the primary therapy. However, even if our results suggest that oncological and reproductive prognoses in patients with AH are slightly better than those in patients with EC, they also show that conservative progestin treatment entails a risk of disease progression for both diagnoses.

Disclosure Summary

The Authors have nothing to disclose.

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Conflicts of Interest

The Authors report no financial or commercial conflicts of interest.

Details of Ethics Approval

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