



Impact of obesity on the results of fertility-sparing management for atypical hyperplasia and grade 1 endometrial cancer[☆]



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HIGHLIGHTS

- We studied the impact of obesity on oncologic and reproductive outcomes in women treated conservatively for atypical hyperplasia and endometrial carcinoma.
- Similar response and recurrence rates were observed in obese and non-obese patients.
- Pregnancy rate was higher in non-obese patients in comparison with obese patients.

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ABSTRACT

Objectives. The aim of the present study was to evaluate the impact of obesity on reproductive and oncologic outcomes on the success of fertility-sparing management.

Methods. This retrospective multicenter cohort study included women treated conservatively for atypical hyperplasia (AH) and endometrial cancer (EC) to preserve fertility. Five inclusion criteria were defined: (i) the presence of AH or grade 1 EC confirmed by two pathologists; (ii) adequate radiological examination before conservative management; (iii) available body mass index (BMI) at the beginning of treatment; and (iv) a minimum follow-up time of six months.

Results. Forty patients fulfilled the inclusion criteria (17 had EC, and 23 had AH), mean age and BMI were 33 years and 29 kg/m² respectively. Among the 15 obese patients, after medical treatment, 10 patients responded (67%) and three relapsed, whereas in the 25 non-obese patients, 19 responded (76%) and three relapsed ($p = 0.72$). The overall pregnancy rate and follow-up time were 35% and 35 months respectively. Among the 15 obese patients, after medical treatment, two patients became pregnant, whereas in the 25 non-obese patients, 12 became pregnant ($p = 0.04$).

Conclusion. Despite similar response and recurrence rates, our results suggest that fertility-sparing management for AH and EC is associated with a lower probability of pregnancy in obese patients.

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Introduction

Endometrial carcinoma (EC) and atypical hyperplasia (AH) classically affect postmenopausal women. However, approximately 5% of patients are diagnosed with these diseases before they are 40 years old [1]. The classic treatment requires, at a minimum, a hysterectomy with a bilateral salpingo-oophorectomy; however, the safety of a conservative approach has been confirmed in several cohort studies that

evaluated uterine preservation [2]. Therefore, conservative treatment should be discussed in young patients who wish to preserve their fertility.

For more than 40 years, the fertility-sparing management of EC and AH and its oncologic and reproductive outcomes have been reported in the literature. Young women with AH or EC typically present with a history of infertility, obesity, chronic anovulation, and polycystic ovarian syndrome (PCOS), which are all conditions associated with prolonged and unopposed estrogen exposure [3]. However, none of these characteristics have been studied as possible prognostic factors for the oncologic and reproductive outcomes of fertility-sparing management. In particular, the impact of obesity has never been evaluated. Recently, a body mass index (BMI) of 35 or higher has been suggested to be

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associated with a failure to regress and the relapse of complex hyperplasia treated with a levonorgestrel IUD [4]. There was no impact of BMI on the outcomes of patients treated with oral progestogens. Unfortunately, the authors included both women wishing to preserve their fertility and those who were unfit for surgery. Similarly, both complex nonatypical hyperplasia and atypical complex hyperplasia were included. Those two pathological entities do not have the same prognosis because their risks for progression to carcinoma, without intervention, are 3% for complex nonatypical hyperplasia and up to 29% for women with complex atypical hyperplasia [5]. In a more recent prospective study including 289 patients with AH, the rate of concurrent endometrial carcinoma reached 43% [6].

Their treatment is also usually different: complex nonatypical hyperplasia often leads to treatment with a levonorgestrel IUD or oral progestogens, whereas hysterectomy is the indicated treatment for complex atypical hyperplasia [7].

Previous studies have shown reduced fertility in obese women [8], but the possibility of fertility-sparing management of AH and EC in obese women has never been evaluated; as a result, their pregnancy probability remains unknown. Uterine preservation is mainly proposed for young women who wish to achieve pregnancy (contraindication to hysterectomy in young women is rarely observed), and the success of such a strategy must take into account the pregnancy probability, as well. If the pregnancy probability in obese young women was particularly low in comparison to that of non-obese patients, this evidence could support the renunciation of uterine preservation or the need for a rapid loss of weight during the fertility-sparing management of obese patients. The aim of the present study was to evaluate the impact of obesity on reproductive and oncologic outcomes on the success of fertility-sparing management.

Methods

We conducted a retrospective multicenter analysis of patients with AH and EC who were managed conservatively between 2001 and 2012 in ten French gynecological units. For each patient, data on the clinical characteristics, surgical management and patient outcomes were noted from the medical record.

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 (including a reference pathologist). Patients with grade 2 or 3 EC who were treated conservatively were excluded and reported in another article [9].
- ii. 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 with a suspicion of myometrial invasion on MRI were excluded from the study.
- iii. The patient was followed up for a minimum period of six months.
- iv. BMI was available at the beginning of treatment. It was defined as the individual's body mass divided by the square of their height, with the value given in kg/m². Patients were considered to be obese if their BMI was over 30.

Patients who met the criteria were counseled extensively regarding the risk of recurrence or progression if they chose medical therapy. All desired to preserve the possibility of pregnancy and gave informed consent for the treatment. We excluded all cases that used conservative management due to any concern other than fertility sparing (e.g., a medical contraindication to surgery) from the study.

The patients who met the inclusion criteria were scheduled to receive medical treatment for at least three months. Given that a higher incidence of synchronous ovarian cancer in young patients has been

reported [10], a diagnostic laparoscopy was performed prior to medical treatment in the last 27 patients. In no case did laparoscopic findings modify disease staging. Because the lymph node metastatic risk in grade 1 EC limited to the endometrium is close to zero [11], no lymphadenectomy was performed. All patients included in this study were assessed for infertility prior to conservative management.

Response was assessed using the pathological specimens obtained at curettage or endometrial biopsy after 3–6 months of medical therapy. Remission was indicated if the last endometrial sample or hysterectomy specimen showed normal endometrium without hyperplasia. Persistence was indicated if the last biopsy showed AH or EC when the entry biopsy showed AH or grade 1 EC. Recurrence was indicated if a lesion that had initially regressed following treatment reappeared. For patients showing no response to medical therapy, the plan was to propose total hysterectomy with or without bilateral salpingo-oophorectomy. If the patient wished to continue the fertility sparing management and if no progression was diagnosed, a secondary medical therapy different from the first used was attempted. For example, if no remission occurred after 3–6 months of progestin therapy, GnRH agonist could be given.

After the documentation of complete remission, women were followed up every 3–6 months with diagnostic hysteroscopy and endometrial biopsies. Patients were encouraged to conceive spontaneously. Assisted reproductive technology (ART) could be attempted after complete remission and was based on the couple's fertility parameters. Women with anovulation or PCOS were candidates for ovulation induction using clomiphene acetate or in vitro fertilization (IVF), and couples with spermatid disorders were more likely to undergo intracytoplasmic sperm injection (ICSI). Women who failed in their attempts to conceive or who successfully completed childbearing were encouraged to undergo definitive surgery.

Statistical analysis

The Fisher exact test and two-sided *t*-test were employed for statistical analysis. Significance was held at the standard value of $p < 0.05$. Kaplan–Meier curves were generated to examine the remission and pregnancy probabilities. Recurrence was not studied for survival because it only concerns those who underwent remission and it is a rare event in women treated conservatively for AH and EC to preserve fertility.

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

Patient population, management and follow-up

Forty patients were included in the study: 15 obese and 25 non-obese patients with AH or EC. None of the patients had a family history consistent with hereditary nonpolyposis colon cancer according to the Amsterdam II definition [12]. Patient, pathological and treatment characteristics are summarized in Table 1.

The patients' ages ranged from 23 to 40 years. The obese patients were significantly younger than the non-obese patients ($p = 0.04$). Most patients did not have previous pregnancies (77.5%). The diagnosis of endometrial lesions was performed during investigations of infertility in 27 cases (67.5%) and irregular bleeding in the remaining 13 cases (32.5%). The obese patients presented with an associated infertility factor (mainly PCOS) more frequently than the non-obese patients (11/15 and 8/25, respectively, $p = 0.02$). In both obese and non-obese patients, the diagnosis was more frequently made during infertility investigations.

The proportions of EC and AH were comparable in obese and non-obese patients (5 AH/10 EC and 13 AH/12 EC, respectively, $p = 0.51$).

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