

Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis

Martin Koskas, M.D.,^{a,b,c,d} Jennifer Uzan, M.D.,^a Dominique Luton, M.D., Ph.D.,^{a,b} Roman Rouzier, M.D., Ph.D.,^{d,e} and Emile Daraï, M.D., Ph.D.^{c,f}

^a Department of Obstetrics and Gynecology, Bichat University Hospital, Paris, France; ^b Paris Diderot University, Paris, France; ^c Unité Mixte de Recherche S938, Université Pierre et Marie Curie, Paris, France; ^d Equipe d'accueil 7285, Université de Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France; ^e Department of Gynecology, Institut Curie, Paris, France; and ^f Department of Obstetrics and Gynecology, Tenon University Hospital, Paris, France

Objective: To evaluate the various possible prognostic factors on the fertility-sparing management of atypical hyperplasia and endometrial cancer; to generate survival curves to estimate remission and recurrence rates according to time.

Design: Systematic review and meta-analysis. Registration number: CRD42013004557.

Setting: University hospital.

Patient(s): Patients who underwent fertility-sparing management for atypical hyperplasia and endometrial cancer.

Intervention(s): All published studies were identified through MEDLINE and reported according to PRISMA guidelines.

Main Outcome Measure(s): Remission, recurrence, progression, and pregnancy rates by age, obesity, infertility, previous pregnancy, histology, and medical treatment.

Result(s): A total of 370 patients from 24 studies were included. The 12- and 24-month remission probabilities were 78.0% and 81.4%, respectively. In multivariate analysis, previous pregnancy (odds ratio [OR] 2.70, 95% confidence interval [CI] 1.23–5.89), infertility (OR 2.26, 95% CI 1.05–4.87), and treatment with megestrol acetate (OR 2.70, 95% CI 1.20–6.02) were associated with higher remission probability. The 12- and 24-month recurrence probabilities were 9.6% and 29.2%, respectively. In multivariate analysis, none of the factors studied was associated with higher recurrence probability. Twenty-two studies totaling 351 patients were used to assess pregnancy rate; 111 subjects (32%) had one pregnancy or more. In multivariate analysis, none of the factors were associated with pregnancy probability. Among the 263 patients used to assess progression rate, 39 (15%) had a tumor with at least myometrial invasion on the hysterectomy specimen. Endometrial cancer and the use of other medical therapies (in comparison with megestrol acetate) were associated with an increased probability of progression.

Conclusion(s): Fertility-sparing management should not be contraindicated in older patients with previous infertility or obesity. (Fertil Steril® 2014;101:785–94. ©2014 by American Society for Reproductive Medicine.)

Key Words: Fertility sparing, conservative, endometrial cancer, endometrial atypical hyperplasia, systematic review

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Received July 14, 2013; revised November 15, 2013; accepted November 19, 2013; published online January 2, 2014.

M.K. has nothing to disclose. J.U. has nothing to disclose. D.L. has nothing to disclose. R.R. has nothing to disclose. E.D. has nothing to disclose.

Reprint requests: Martin Koskas, M.D., Department of Gynecology, Bichat University Hospital, 46 rue Henri Huchard, 75018 Paris, France (E-mail: martin.koskas@wanadoo.fr).

Fertility and Sterility® Vol. 101, No. 3, March 2014 0015-0282/\$36.00
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<http://dx.doi.org/10.1016/j.fertnstert.2013.11.028>

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 least 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 (2–4). Therefore, conservative treatment should be discussed in 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. However, because these studies were performed on small patient cohorts, they lack the statistical power to establish guidelines concerning the management and prognosis of conservative AH and EC treatments.

Young women with AH or EC typically have a history of infertility, obesity, chronic anovulation, and polycystic ovarian syndrome (PCOS), which are all conditions associated with prolonged unopposed estrogen (E) exposure (5). However, none of these characteristics have been studied as possible prognostic factors for the oncologic and reproductive outcomes of fertility-sparing management.

Previous studies have shown reduced fertility in obese women (6), but the possibility of fertility-sparing management in obese women has never been evaluated. Similarly, in contrast to the study performed by Fauvet et al. (7), which focuses on ovarian borderline tumors, the impact of age has not been evaluated in terms of the reproductive outcome of fertility-sparing management of AH and EC.

Hormone therapy is usually administered to promote remission and allow pregnancy. Although several prospective studies have been conducted to evaluate the safety of this approach, none of these studies have compared different treatment or regimen protocols. Oral progestin has frequently been evaluated, in particular 17-hydroxyprogesterones such as medroxyprogesterone acetate (MPA) (4) and megestrol acetate (MA) (8). Other therapies that have been evaluated in a limited number of cases include GnRH agonist (9), intrauterine devices (IUDs) containing progestogen (10), or a combination of these therapies (11).

A recent review (3) showed that AH has a significantly higher response rate than grade 1 EC, and a lower remission rate is observed in women with carcinoma than in those with hyperplasia. Nonetheless, the reproductive outcomes did not differ. This review focused on the outcomes and the comparison of AH and EC for the fertility-sparing management of EC and AH. Notably, possible prognostic factors that may affect oncologic and reproductive outcomes were not studied.

The aim of this review was to evaluate the impact of age, gravidity, obesity, fertility, histology, and hormonal treatments on reproductive and oncologic outcomes to better predict the success of fertility-sparing management. Several factors need to be investigated to adequately assess the optimal conditions for fertility-sparing treatment of AH and EC; these factors include timing, the optimal duration of treatment, and when to consider hysterectomy if the patient does not become pregnant. The duration of fertility-sparing treatment should be based on a balance between remission and pregnancy while avoiding recurrence and/or progression. For this reason, we have built survival curves. Moreover,

this approach allows for a better understanding of the evolution of medically treated EC and AH.

MATERIALS AND METHODS

Studies Eligible for Review

The population of interest in this systematic review was women with AH or EC that was limited to the endometrium (1988 International Federation of Gynecology and Obstetrics stage IA). The intervention queried was fertility-sparing therapies, and the outcomes were evidence of disease regression, relapse, pregnancy, and disease progression. We conducted a research with MEDLINE (1950 to 2011) using a combination of medical subject headings. Text words were used to generate two subsets of citations: [1] studies of EC (“endometri* cancer*,” “malignant endometri*,” “endometri* carcino*”) or AH (“endometri* atypical hyperplas*,” “pre-malignant endometri*,” “precancer* endometri*”) and [2] studies of fertility-sparing therapies such as progestogens and IUDs or systems (“intrauterine devices medicated,” “levonorgestrel,” “Mir-ena,” “intrauterine progest*,” “LNG-IU*,” “progest*,” “gestag*,” “fertility-sparing therapy,” “conservative therapy,” “hormon* therapy,” “conservative management”). These subsets were combined with the word “and” and limited using the terms “humans” and “female” to generate a subset of citations. The reference lists of all known primary and review articles were examined to identify cited articles that were not captured by electronic searches. Only articles published in English and involving women between 19 and 44 years of age were retrieved.

Inclusion and exclusion criteria for the selection of articles were as follows. Inclusion criteria were studies including patients between 19 and 44 years of age; fertility-sparing management; and histologic diagnosis of AH or stage I adenocarcinoma of the endometrium. Exclusion criteria were case reports and small study series with fewer than five patients; articles not written in English; patients with tumor invading the myometrium; conservation because of high risk for perioperative morbidity; data not extractable; other uterine neoplasia than endometrioid adenocarcinoma; patients with simple hyperplasia; and redundant articles.

All studies obtained as a result of the search were reviewed. The original portable document files of studies obtained from the search were located through direct online links to the files from the search results.

The complete review protocol can be accessed online (<http://www.crd.york.ac.uk/prospere>); the registration number is CRD42013004557.

Data Abstraction

Each of the 24 articles were read by two different readers (J.U. and M.K.), and a database was created with the following two types of items: [1] the possible prognostic factors for fertility preservation management (because no standard guidelines exist for this management, a control group could not be constituted), and [2] four outcomes to assess the efficacy of this strategy. Studies containing original and detailed data on the management and oncologic and reproductive

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