GENERAL GYNECOLOGY

Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis

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OBJECTIVE: The objective of the study was to evaluate the regression, relapse, and live birth rates of early-stage endometrial cancer (EC) and atypical complex hyperplasia (ACH) with fertility-sparing treatment.

STUDY DESIGN: This was a metaanalysis of the proportions from observational studies with a random-effects model and a meta-regression to explore for heterogeneity.

RESULTS: Thirty-four observational studies, evaluating the regression, relapse, and live birth rates of early-stage EC (408 women) and ACH (151 women) with fertility-sparing treatment. Fertility-sparing treatment for EC achieved a pooled regression rate of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28%. For ACH the pooled regression rate was 85.6%, a relapse rate of 26%, and a live birth rate of 26.3%. Twenty women were diagnosed with ovarian cancer (concurrent or metastatic) during follow-up (3.6%) and 10 progressed to higher than stage I EC (1.9%) from which 2 women died.

CONCLUSION: Fertility-sparing treatment of EC and ACH is feasible and selected women can satisfy their reproductive wishes.

Key words: atypical complex hyperplasia, endometrial cancer, fertility-sparing treatment, live births, progestogens

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In 2007, 7536 women in the United Kingdom were diagnosed with endometrial cancer (EC) and 239 of these women were younger than 45 years old (3.2%).[1] Often these women have strong fertility desires because anovulatory infertility is strongly associated with the development of EC and atypical complex hyperplasia (ACH).[2] It is known that these women are usually diagnosed with early clinical stage, well-differentiated EC, which carries a good prognosis. Traditionally, it is recommended that these women undergo a staging abdominal hysterectomy. However, multiple studies suggest that in selected women with early clinical stage disease, this can be managed with fertility-sparing hormonal therapy.

★ EDITORS' CHOICE ★

The use of progestogens can induce endometrial regression and prevent the progression of the disease. Oral progestogens are used to treat EC and ACH, but more recently, the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena, Bayer, Berkshire, UK) has also been used successfully to treat ACH.[3] These options are also popular among clinicians for women who decline hysterectomy.[4] Yet there is significant uncertainty about the efficacy of these therapies from observational studies with small sample sizes, which makes it difficult to counsel the women accordingly. To ascertain the efficacy of these therapies, we conducted a systematic review of observational studies evaluating the regression, relapse, and live birth rates for the treatment of EC and ACH, and we performed a metaanalysis of their treatment effects.

Materials and Methods

Identification of literature

The population of interest in this systematic review was women with early clinical stage (International Federation of Gynecology and Obstetrics stage I) EC or ACH, the intervention was fertility-sparing therapies, and the outcome was evidence of disease regression, relapse, and live births. The following electronic databases were searched: MEDLINE (1950 to September 2011), EMBASE (1980 to September 2011), Cochrane Central Register of Controlled Trials and Web of Science conference proceedings

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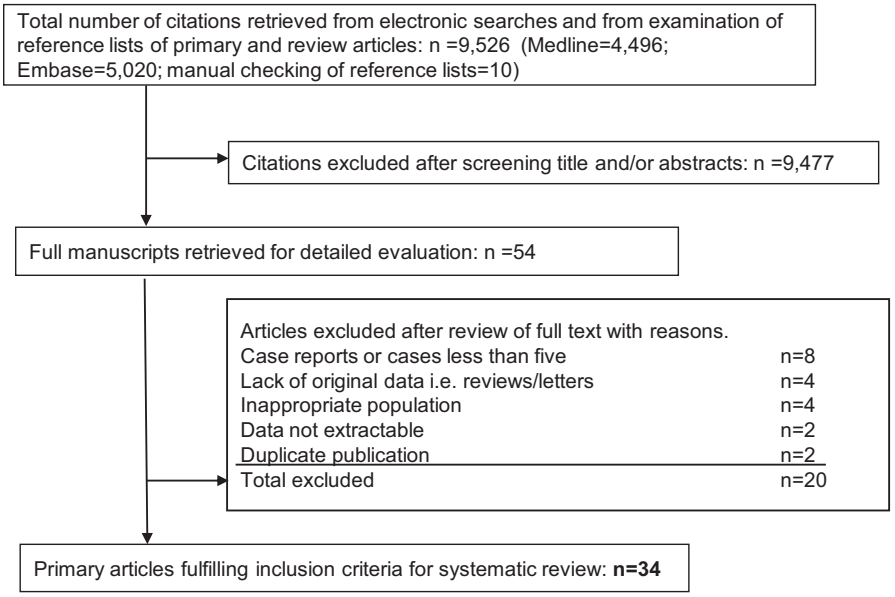
FIGURE 1
Study selection process



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.

(ISI Proceedings, 1990 to September 2011).

A combination of medical subject headings (MeSH) and text words were used to generate 2 subsets of citations, 1 including studies of EC ("endometr* cancer,*" "malignant endometr*") or endometrial hyperplasia ("endometr* hyperplas,*" "premalignant endometr,*" "precancer* endometr*") and the other including studies of fertility-sparing therapies such as progestogens and intrauterine devices or systems ("intrauterine devices medicated," "Levonorgestrel," "Mirena," "intrauterine progest,*" "LNG-IU,*" "progest,*" "gestag,*" "fertility-sparing therapy," "conservative therapy," "hormone* therapy").

These subsets were combined with the word "and" and limited to the words "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 not captured by electronic searches. Language or geographical restrictions were not applied during the search or selection.

Study selection and data extraction

Studies were selected if the participants were women diagnosed histologically with early clinical stage EC or ACH, the intervention was fertility-sparing therapy, and the outcomes were histological disease regression, relapse, or live birth rates. Case reports or series with fewer than 5 cases were excluded. Studies classifying women with endometrial hyperplasia in other than the World Health Classification 1994[5] (simple, complex, and atypical) were also excluded.

Studies were selected in a 2-stage process. First, the titles and abstracts from the electronic searches were scrutinized by 2 reviewers independently (I.D.G. and J.Y.), and full manuscripts of all citations that met the predefined selection criteria were obtained. Second, final inclusion or exclusion decisions were made on the examination of the full manuscripts. In cases of duplicates, the most recent or the most complete publication was used. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (A.C.). Two reviewers (I.D.G. and J.Y.) completed the quality assessment. The Methodological Index for Non-Randomised Studies (MINORS), which assesses the quality of the included studies, was implemented.[6] From each study, outcome data were extracted in 2 × 2 tables by the 2 reviewers (I.D.G. and J.Y.).

Disease regression was defined as a lack of residual EC or complex hyperplasia during follow-up endometrial sampling. Disease relapse was defined EC or complex hyperplasia diagnosis during follow-up endometrial sampling following an endometrial sample that showed disease regression. Live births was defined as the birth of healthy infants during the follow-up period, and its rate was calculated as the number of women who had a birth of healthy infants divided by the number of total of women undergoing fertility-sparing therapy. We also counted the number of women who were diagnosed with concurrent or metastatic ovarian cancer or upgraded disease to higher than stage I and deaths from this disease during follow-up.

Statistical analysis

Regression, relapse, and live birth rates were extracted from each study, and we computed the log of the ratio and its corresponding standard error for each study. We performed the metaanalysis using inverse-variance weighting to calculate the random-effects summary estimates.[7] We obtained an estimate of the between-study variance with a random-effects metaanalysis. The square root of this number is the estimated SD of the underlying effects across studies.

Because we had relative measures of effect, the confidence intervals were centered on the natural logarithm of the pooled estimate and the limits exponentiated to obtain an interval on the ratio scale.[8] Forest plots were created for each outcome, showing individual study proportions with confidence intervals (CIs) and the overall DerSimmonian-Laird pooled estimate.[9] Heterogeneity of the treatment effects was assessed graphically with forest plots and statistically analyzed using the χ^2 test.[10] Exploration of the causes of heterogeneity for the live birth rate was planned according to the reproductive method, and it was assessed with the aid of meta-regression.[11] Statistical analyses were performed using Stata 8.0 (StataCorp, College Station, TX).