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Full length article

Complex non atypical hyperplasia and the subsequent risk of carcinoma, atypia and hysterectomy during the following 9–14 years

Maja Lundegaard Iversen*, Margit Dueholm

Department of Obstetrics and Gynecology, Aarhus University Hospital, Palle Juul-Jensens Blvd. 99, 8200, Aarhus N, Denmark

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ABSTRACT

Introduction: The aim of this study was to evaluate the long-term risk of developing atypical hyperplasia/endometrial cancer or having a hysterectomy after being diagnosed with complex non-atypical hyperplasia (CH).

Material and method: A historic cohort study of 114 women diagnosed with CH between January 1st 2000 and December 31st 2005. All patient records and pathologic reports were reviewed with complete follow up on all patients in the national pathologic database until September 1st 2014.

Kaplan-Meier analysis was used to determine (1) no hysterectomy and (2) no diagnosis of endometrial cancer or atypia after the CH diagnosis.

Results: 15% (n = 17) were diagnosed with endometrial cancer and 7% (n = 8) with atypia, most during the first year (10 cancer, 7 atypia). 9% (8/85) of the remaining women at risk developed cancer or atypia in the follow-up period after one year. By Kaplan-Meier the five-year risk for cancer or atypia was 20% (CI; 14–21). The risk of having undergone hysterectomy within five years was 30% (CI; 22–39).

Conclusion: The long-term risk of being diagnosed with atypia or cancer after a CH diagnose is not insignificant, when disregarding patients having undergone hysterectomy. More than half the women with atypia or cancer are diagnosed or operated during the first year. This could indicate the presence of concomitant but unidentified cancer or atypia at the time of initial sampling. This study reinforces the importance of follow up or treatment of women with CH – especially, but not only during the first year.

Key message: The risk of having a hysterectomy or diagnosed with atypical hyperplasia/cancer endometrie is high after a diagnosis of complex hyperplasia without atypia.

Introduction

Endometrial hyperplasia is reported to be present in 2–10% of premenopausal women, 5% of perimenopausal women [1] and 10% of postmenopausal women with abnormal uterine bleeding. Hyperplasia may progress to malignant disease depending on the grade of the hyperplasia [2].

The grade of hyperplasia is most commonly classified according to the World Health Organisation (WHO) 1994 classification system. It is based on architectural and cytological alterations in histological findings. Hyperplasia is classified as simple hyperplasia without atypia (SH), complex hyperplasia without atypia (CH) and simple or complex hyperplasia with atypia (AH). The classification is subjective and has a low reproducibility between pathologists [3]. Another issue illustrated in a review by Lacey, is that approximately 50% of women diagnosed with AH have concurrent carcinoma [4]. Moreover AH often seem to progress to carcinoma [2] and hysterectomy is recommended in women with AH past the childbearing age. The risk of concomitant carcinoma and progression to cancer is lower in women with a diagnosis of CH [2]. Treatment with oral progestin and gestagen IUDs are effective [1,5]. Moreover follow-up is often recommended, but so far, no evidence based standardized treatment guidelines exist [4].

Several studies have evaluated the risk of cancer development in women with hyperplasia without atypia. The most cited study from Kurman based on only 29 patients with CH, 3% presented with cancer progression during 10–20 years [2]. Most studies include less than 70 patients with CH, and furthermore the follow up period is very short [5–14]. Furthermore, when calculating the risk, no study correct for the numbers of hysterectomies or deaths which may include a large proportion of the women at risk in the follow-up period and thereby the risk could be underestimated.

Abbreviations: CH, complex hyperplasia without atypia; SH, simple hyperplasia without atypia; AH, simple or complex hyperplasia with atypia; IUD, intrauterine device.

* Corresponding author.
E-mail address: maja.lundegaard.iversen@vest.rm.dk (M.L. Iversen).

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The aim of the current study was to evaluate the long-term risk of developing atypical hyperplasia/endometrial cancer or having a hysterectomy after being diagnosed with complex endometrial hyperplasia without atypia in a general gynaecologic setting.

Materials and methods

This study is a historic cohort study of 114 women identified with complex hyperplasia without atypia between January 2000 and December 2005.

191 patients where identified with the pathological diagnose of complex hyperplasia, between January 1st 2000 and December 31st 2005 from the pathological departments in Holstebro and Aarhus, Denmark.

These findings were diagnosed by either general pathologists or trained oncopathologists.

All patient records and pathology reports were reviewed. All pathology reports in Denmark are registered by the patient's civil registration number (CRN). Complete coverage of all readmissions in the whole country was obtained by use of the patients' CRNs. We checked for admissions to other institutions with the central pathology database and identified any other procedures performed at other centres during the follow-up period.

77 women were not found eligible for this study. We excluded 20 patients because they had the CH diagnose in hysterectomy specimens and could therefore not be followed. 57 were excluded because of wrong registration of the diagnosis. After detailed review of the pathology report they had simple hyperplasia, atypical hyperplasia, endometrial cancer or uncertainty about the diagnose and undefined hyperplasia. They were also excluded if they had an earlier sample with atypia.

114 patients fulfilled all the criteria for inclusion: a diagnosis of CH and no hysterectomy at initial sample, no atypia and no endometrial cancer in current or previous samples.

Follow-up information was taken from the patient's records and from Patoweb (The Danish national register for pathological diagnosis). The Patoweb includes complete information on all pathology specimens obtained in Denmark. Pathology reports of all endometrial or uterine specimens in the follow up period were reviewed. We recorded all pathology reports on specimens in the period: date, type (dilatation and curettage (D&C), endometrial sample (pipelle, milex or vabra), hysteroscopic sample including transcervical resections, hysterectomy, not specified and no sample) diagnose (benign without hyperplasia, SH, CH, AH and endometrial cancer). The indication (postmenopausal bleeding, menoragia, metroragia, menometroragia, control, other, not specified) and treatment (no treatment, oral progestins, gestagen IUD, removal of HRT (hormone replacement treatment), hysterectomy, unknown) of each pathologic sample was obtained from patient records. The patient's record was reviewed for information on age, menopausal status, weight, height, comorbidity (diabetes, PCOS, anovulation), number of birth, indication for the sample, and treatment. Data collection ended September 1st 2014.

This study is a retrospective study, and according to Central Denmark Region Committee on Biomedical Research this project was not required to be formally approved at the institution and no written patient informed consent was obtained. The Danish Data Protection Agency approved.

Statistic

Statistical analysis was performed by using Stata version 11 software. Kaplan-Meier analysis was performed to determine 1: freedom from hysterectomy and 2: freedom from endometrial cancer or atypia. These women entered the study at the day of diagnosis of complex hyperplasia. The time of observation ended at the date of hysterectomy, when performed. The time in observation for women without hysterectomy ended on the last date of database verification (September 1st 2014), or the day they died. Cox proportional hazard regression analysis was used to test whether age was related to development of cancer. Women were divided into groups over and below 65 years of age, and the different groups of treatment options. Differences between age groups and treatment options and relation to cancer and atypia were tested for significance by using the associated log-rank test.

Results

The characteristics of the patients are seen in Table 1.

Indication for endometrial sample was postmenopausal bleeding in 42% of patients, and most women had abnormal uterine bleeding (78%). 21 (18%) only had a single baseline sample during follow up and other had from two to six samples. In total, 107 D&C, 60 hysteroscopies and 63 endometrial samples were performed in these women during follow-up. In the group of patients who developed atypia or endometrial cancer the mean age was 58.7 ± 12.2 and most 17 (68%) were postmenopausal. The mean age of women supposed to be premenopausal ($\leq$51 years old) were

Table 1
Characteristic of women.

n = 114	Numbers [mean]	Percentage% [±sd]
Age	[59.1]	[13.1]
Menopausal status:		
Premenopausal	27	23%
Postmenopausal	67	58%
Perimenopausal	20	17%
Indications:		
Abnormal bleeding	89	78%
Control	2	2%
Other given reasons or unknown	23	20%
Sampling methods:		
Curretage	54	47%
Endometrial biopsy(pipelle/vabra)	35	30%
Hysteroscopic biopsy	20	18%
Trans cervical hysteroscopic endometrial resection	2	2%
Treatment in the follow up period		
Gestagen IUD	8	7%
Oral progestins	20	17,5%
Removal of hormone replacement therapy	8	7%
Hysterectomy	41	36%