Risk factors for atypical hyperplasia and endometrial cancer in the infertility population: a case-control study

Jenna L. Kahn, M.D.,[a] Lindsey Buckingham, M.D.,[b] Nathanael C. Koelper, M.S.,[c] Mary D. Sammel, Sc.D.,[c] and Divya K. Shah, M.D., M.M.E.[d]

[a] Department of Obstetrics and Gynecology, Pennsylvania Hospital, University of Pennsylvania, Philadelphia, Pennsylvania; [b] Division of Gynecologic Oncology, University of North Carolina, Chapel Hill, North Carolina; and [c] Department of Biostatistics, Epidemiology and Informatics and [d] Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Pennsylvania, Philadelphia, Pennsylvania

Objective: To estimate the incidence and identify risk factors for atypical endometrial hyperplasia (AH) and endometrial cancer (EC) in American women undergoing infertility evaluation.
Design: Case-control study.
Setting: Academic reproductive endocrinology and infertility practice.
Patient(s): Female patients (18–50 years) seeking infertility evaluation from January 1, 2009 to December 1, 2018. Patients with known genetic predisposition to cancer or prior cancer diagnosis were excluded. Cases were defined as patients diagnosed with AH or EC during infertility workup (n = 22). Controls without AH or EC were randomly selected in a 10:1 ratio (n = 220) from all women undergoing infertility evaluation in the same year.
Intervention(s): None.
Main Outcome Measure(s): Incidence of AH or EC and odds of AH or EC accounting for age, race, body mass index (BMI), and ovulatory dysfunction.
Result(s): Twenty-two cases of AH or EC were identified among 11,569 women undergoing infertility evaluation (incidence 2 per 1,000 women, 95% confidence interval [CI] 1.2–2.9 per 1,000). Of these women, 68% had a BMI ≥ 30 kg/m^2 compared with 25% of controls. In multivariable analyses, women with a BMI ≥ 30 kg/m^2 were 5.9 times more likely to be diagnosed with AH or EC (adjusted odds ratio 5.9, 95% CI 2.0–17.2). Women with ovulatory dysfunction were 3.4 times more likely to be diagnosed with AH or EC (adjusted odds ratio 3.4, 95% CI 1.1–10.1).
Conclusion(s): The incidence of AH and EC in a population of women undergoing infertility evaluation is 10 times that in the general population of premenopausal women. Obesity is the strongest independent risk factor for AH and EC in women with infertility. (Fertil Steril Rep® 2021;2:104–8. ©2020 by American Society for Reproductive Medicine.)
Key Words: Endometrial cancer, atypical hyperplasia, infertility, incidence, risk factors

Endometrial cancer (EC) is the most common gynecologic cancer in the United States, with nearly 55,000 new cases diagnosed in 2015 (1). Although most of these patients are postmenopausal, approximately 12% of EC cases are diagnosed before age 50 years and 3.5% are diagnosed in women less than age 40 years (2). The reported incidence of EC in American women less than age 50 years is <0.01% (1). The incidence of its precursor lesion, atypical hyperplasia (AH), is less clearly defined in this population (3). According to the Center for Disease Control national report on uterine cancer, approximately 6,500 premenopausal women were diagnosed in 2015, and this number continues to increase annually (1, 2). As such, it is increasingly important for gynecologic providers to maintain an index of suspicion for both AH and EC in at-risk young women.

Received May 17, 2020; revised October 13, 2020; accepted October 18, 2020.
J.L.K. has nothing to disclose. L.B. has nothing to disclose. N.C.K. has nothing to disclose. M.D.S. has nothing to disclose. D.F.S. reports royalties from Springer Publications and travel reimbursement from ASRM and ABOG.
Reprint requests: Jenna Lipson Kahn, M.D., Department of Obstetrics and Gynecology, Pennsylvania Hospital, 800 Spruce Street, 2 Pine East, Philadelphia, Pennsylvania 19107 (E-mail: jlkahn28@gmail.com).

Fertil Steril Rep® Vol. 2, No. 1, March 2021 2666-3341

https://doi.org/10.1016/j.xfre.2020.10.005

Although some premenopausal women with endometrial cancers present with abnormal uterine bleeding, many are asymptomatic. Uterine cavity evaluation in an asymptomatic patient is rare, except in the case of patients undergoing infertility evaluation. A routine infertility evaluation typically includes an assessment of the uterine cavity and endometrial lining by an hysterosalpingogram (HSG) and/or a transvaginal ultrasound (TVUS). If an abnormality is identified, diagnostic hysteroscopy with endometrial sampling is frequently performed. A routine infertility evaluation, therefore, may be an opportune time to detect AH or EC in young and otherwise asymptomatic patients.

Infertility has been previously identified as a significant risk factor for EC. Proposed etiologies include unopposed estrogen exposure from high rates of anovulation and nulliparity among infertile women (4–6). However, there are limited data on the incidence and risk factors for AH and EC in an infertile population. Objectives of the present study are to [1] estimate the incidence of AH and EC diagnosed on routine infertility evaluation in an urban American population and [2] to separately identify independent risk factors for AH and EC in American women undergoing a routine infertility evaluation.

MATERIALS AND METHODS

The study population included female patients aged 18–50 years who were seen for an infertility evaluation between January 2009 and December 2018 in the Division of Reproductive Endocrinology and Infertility at the University of Pennsylvania and Pennsylvania Hospital. Patients who had a TVUS and/or an HSG were included in the analysis. Patients with a known genetic predisposition to cancer or a prior diagnosis of uterine, ovarian, breast, or colon cancer were excluded.

Cases were defined as patients with a pathology confirmed diagnosis of AH or EC on endometrial sampling. The diagnosis was identified using International Classification of Disease 9 and 10 codes 621.33 (endometrial hyperplasia with atypia), 621.35 (endometrial intraepithelial neoplasm), N85.02 (endometrial intraepithelial neoplasm), 179 (malignant neoplasm corpus uteri—unspecified site), C55 (malignant neoplasm corpus uteri—unspecified site), 182.0 (malignancy corpus uteri except isthmus), and C54.1 (malignant neoplasm of endometrium). The aims of our study were addressed separately due to the descriptive nature of our first aim and the comparative nature of our second aim. Cases were used to calculate the incidence in the population of women undergoing routine infertility evaluation. For our comparative study, controls were defined as women without AH or EC who were diagnosed with any female factor or unexplained infertility. Cases were matched to randomly selected controls in a 1:10 ratio by year of infertility evaluation based on a sample size calculation demonstrating that 10 controls per case provides 80% power to detect an odds ratio of 3.93 for AH or EC with $\alpha = 0.05$ (Supplemental Fig. 1, available online).

Patient demographics, reproductive history, and relevant medical history data were abstracted and entered into a secure REDCap database. Female age was dichotomized as <35 and ≥ 35 years, body mass index (BMI) as <30 and ≥ 30 kg/m^2, and parity as 0 versus ≥ 1 births. Race was categorized as White, African American, and Other for initial data acquisition; however, was later dichotomized to African American and Other for ease of statistical analysis given our small sample size and race distribution. Infertility diagnoses were categorized as diminished ovarian reserve, ovulatory dysfunction, tubal factor, uterine factor, unexplained infertility, and endometriosis. Presence or absence of polycystic ovarian syndrome (PCOS) was documented separately. Other abstracted data included age at menarche (years), oral contraceptive pill use (yes/no) duration of infertility (months), prior fertility treatments (yes/no), history of abnormal uterine bleeding (yes/no), presence of normal versus abnormal imaging results (TVUS and HSG), and pathology results from endometrial sampling obtained during the infertility evaluation. The study was approved by the Institutional Review Board at the University of Pennsylvania.

Statistical analysis

The incidences of AH and EC were calculated by dividing the number of cases by the total population with infertility. Univariate statistics were generated using χ^2 and Fisher's exact test for categorical variables and Student's *t*-test or Wilcoxon rank sum test for continuous variables as appropriate. Logistic regression modeling was used to estimate the odds of AH or EC. Forward selection was used to account for covariates. Tests for colinearity were performed for BMI and ovulatory dysfunction with no collinearity identified in the study population. The final model accounted for age, African American race, BMI, and presence of ovulatory dysfunction. Statistical analysis was performed by using STATA 14.2.

RESULTS

A total of 11,569 women met inclusion and exclusion criteria, 22 of whom were diagnosed with AH or EC, thus defining the incidence of AH or EC as 2 per 1,000 women (95% confidence interval [CI] 1.2–2.9 per 1,000 women). Of these 22 cases, 12 were diagnosed with AH (incidence 0.10%) and 10 were diagnosed with EC (incidence 0.10%). All women with EC had FIGO (International Federation of Gynecology and Obstetrics) staging system grade I endometrioid adenocarcinoma at time of diagnosis.

Demographics of the cases and controls are shown in Table 1. The median age of cases and controls was 35 years (interquartile range 32–38 years) and 34 years (interquartile range 31–37 years), respectively. Sixty-four percent of women in the cohort were White, 21% African American, and 15% Other races. African American women were overrepresented among cases (n = 8/22, 36%) compared with controls (n = 43/220, 20%). Cases were also significantly more likely to be obese (15/22, 68% vs. 54/220, 25%). Unadjusted analysis also demonstrated higher rates of nulliparity (21/22, 95% vs. 173/220, 79%), chronic hypertension, (6/22, 27% vs. 17/220, 8%), and diabetes mellitus (2/22, 9% vs. 6/220, 3%) among cases compared with controls, although absolute numbers were small in several cells.

TABLE 1

Demographic characteristics of the study population.

Characteristic	Cohort (n = 242)	Controls (n = 220)	Cases (n = 22)	*P* value
Age (y)	34 (31–37)	34 (31–37)	35 (32–38)	.601
Race				
White	156 (64)	144 (65)	12 (55)	.065
African American	51 (21)	43 (20)	8 (36)	
Other	35 (15)	33 (15)	2 (9)	
BMI $\geq$30 kg/m^2	69 (29)	54 (25)	15 (68)	$<$.001
Nulliparous	194 (80)	173 (79)	21 (95)	.088
Previous OCP use	104 (44)	97 (45)	7 (32)	.246
Current smoker	39 (16)	33 (15)	6 (27)	.135
Diabetes	8 (3)	6 (3)	2 (9)	.158
Hypertension	23 (10)	17 (8)	6 (27)	.003
Hypothyroidism	37 (15)	33 (15)	4 (18)	.699

Note: Data are reported as median (interquartile range). All other data are reported as n (%). BMI = body mass index; OCP = oral contraceptive pill.

Kahn. Endometrial cancer risk in patients with infertility. Fertil Steril Rep 2020.

Reproductive characteristics of cases and controls are described in Table 2. Cases had a longer duration of infertility (23 vs. 12 months) compared with controls. Cases were more likely to be diagnosed with ovulatory dysfunction (11/22, 50% vs. 56/220, 25%), likely due to a higher prevalence of PCOS (8/22, 36% vs. 42/220, 19%). The etiologies of ovulatory dysfunction among cases were limited to PCOS, pituitary dysfunction, hypothyroidism, and obesity, most of which (73%) were secondary to PCOS. There were no cases with ovulatory dysfunction attributable to hypothalamic hypogonadism. Cases were also more likely to report abnormal uterine bleeding (12/22, 55% vs. 34/220, 34%), have an abnormal HSG (12/22, 55% vs. 31/220, 31%), and/or an abnormal TVUS (15/22, 68% vs. 52/220 24%) compared with controls.

Results of the logistic regression are shown in Table 3. After adjusting for age, African American race, and presence of ovulatory dysfunction, women with BMI $\geq$30 kg/m^2 were 5.9 times more likely to be diagnosed with AH or EC (adjusted odds ratio [AOR] 5.9, 95% CI 2.0–17.2). Patients with ovulatory dysfunction were 3.4 times more likely to be diagnosed with AH and/or EC (AOR 3.4, 95% CI 1.1–10.1) when controlling for age, African American race, and BMI. Patient age and African American race were not independently associated with odds of AH or EC after controlling for BMI. When analyses were stratified by BMI, patients with ovulatory dysfunction and BMI $\geq$30 kg/m^2 were 7.25 times more likely to be diagnosed with AH and/or EC (AOR 7.25, 95% CI 1.6–32.1). In women with normal BMI and ovulatory dysfunction, we found that there was no significant association with a diagnosis of AH and/or EC (AOR 0.68, 95% CI 0.07–7.01) (Table 4). When analyses were stratified by presence of ovulatory dysfunction, patients with ovulatory dysfunction and BMI $\geq$30 kg/m^2 were significantly more likely to be diagnosed with AH and/or EC (AOR 23.30, 95% CI 2.32–233.97). Obese patients without ovulatory dysfunction also trended toward an increased risk for AH and/or EC, but the confidence interval was broad and not found to be statistically significant (AOR 3.11, 95% CI 0.80–12.18) (Table 4). Given the complex relationship between these two risk factors, a Pearson correlation coefficient analysis was

TABLE 2

Reproductive characteristics of the study population.

Characteristic	Cohort (n = 242)	Controls (n = 220)	Cases (n = 22)	*P* value
Duration of infertility (mo)	12 (9–24)	12 (9–24)	23 (12–36)	.068
Infertility diagnosis				
Diminished ovarian reserve	53 (22)	49 (22)	4 (18)	.658
Ovulatory dysfunction	67 (28)	56 (25)	11 (50)	.014
Tubal factor	29 (12)	28 (13)	1 (5)	.488
Uterine factor	45 (19)	39 (18)	6 (27)	.273
Unexplained	83 (34)	80 (36)	3 (14)	.032
Endometriosis	16 (7)	14 (6)	2 (9)	.624
PCOS	50 (21)	42 (19)	8 (36)	.056
History of AUB	83 (36)	71 (34)	12 (55)	.054
Prior fertility treatment	46 (11)	40 (18)	6 (27)	.305
Abnormal HSG	81 (33)	69 (31)	12 (55)	.028
Abnormal ultrasound	67 (28)	52 (24)	15 (68)	$<$.001

Note: Data are reported as median (interquartile range). All other data are reported as n (%). AUB = abnormal uterine bleeding; HSG = hysterosalpingogram; PCOS = polycystic ovarian syndrome.

Kahn. Endometrial cancer risk in patients with infertility. Fertil Steril Rep 2020.

TABLE 3

Multivariate analysis of risk factors for atypical endometrial hyperplasia and endometrial cancer in the population with infertility.

Risk factor	OR	AOR	95% CI	*P* value
BMI ≥30 kg/m^2	6.59	5.88	2.01–17.19	.001
Ovulatory dysfunction	2.93	3.36	1.11–10.18	.032
African American race	2.35	0.814	0.27–2.44	.713
Age	1.03	1.07	0.96–1.19	.198

Note: After adjusting for remaining covariates (age, African American race, BMI ≥30 kg/m^2, ovulatory dysfunction). AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; OR = odds ratio.

Kahn. Endometrial cancer risk in patients with infertility. Fertil Steril Rep 2020.

performed and demonstrated a correlation coefficient of 0.28 for BMI ≥30 kg/m^2 and 0.16 for ovulatory dysfunction.

DISCUSSION

The present study demonstrates an incidence of EC or AH diagnosed on a routine infertility evaluation of 2 per 1,000 women (0.1%), approximately 10 times higher than the reported incidence in comparably aged women in the general population in the United States (1). Adjusted analysis revealed obesity (BMI ≥30 kg/m^2) was the strongest risk factor for developing AH or EC (AOR 5.9, 95% CI 2.0–17.2), independent of age, race, and ovulatory dysfunction. In addition, ovulatory dysfunction was found to be a risk factor with affected patients being 3.4 times more likely to have AH or EC. Although obesity and ovulatory dysfunction were not found to be collinear in the study population, both play a role in the risk of developing AH and/or EC with obesity as the primary driver of this relationship. Stratified analyses further revealed that the risk of AH and/or EC among women with ovulatory dysfunction was modified by BMI. Although women with ovulatory dysfunction and BMI ≥30 kg/m^2 were 7.25 times more likely to be diagnosed with AH and/or EC, no association was seen among those with BMI <30 kg/m^2. Therefore in patients with ovulatory dysfunction, not being obese was protective against an AH and/or EC diagnosis.

Similar to findings in prior studies on EC in the general population, exposure to unopposed estrogen is associated with most cases of AH and/or EC in our population. Our cases were more often nulliparous and had longer duration of infertility compared with controls. Ovulatory dysfunction due to PCOS was more prevalent among cases, and although not statistically significant, this association is relevant clinically when assessing risk factors in patient encounters. Prevalence of chronic hypertension and/or diabetes mellitus diagnoses were also higher among cases, which is likely explained by concurrent obesity. In the general population, oral contraceptive pill use and/or smoking are protective factors against the development of EC; however, this was not demonstrated in our population.

Much of the current knowledge regarding AH and/or EC among reproductive-aged women has been extrapolated from the gynecologic oncology literature on pregnancy outcomes for women with AH and/or EC undergoing fertility-sparing treatment. In one small retrospective cohort study (7) determining the outcomes of fertility-sparing treatment with progestin therapy for AH and EC in women <40 years old, 73% of women reported being diagnosed with infertility. Rackow et al. (5, 6) have suggested that women undergoing infertility evaluation are at increased risk of developing EC compared with age-matched counterparts due to prolonged unopposed estrogen exposure associated with nulliparity, ovulatory dysfunction, PCOS, and/or obesity. In addition, studies suggest that infertility may be more common among young patients with AH or EC due to potentially impaired embryo implantation (5).

There is limited literature on AH and EC diagnosed incidentally among patients presenting for an infertility workup, and no studies have examined this question in an American population. Fujiwara et al. (8) describe six cases of AH and/or EC found within 19,826 women undergoing routine infertility investigations in Japan between 2007 and 2016. They reported an incidence of 0.03% and 0.02% for AH and EC, respectively, in their population, which is 5–10 times higher than the overall incidence in Japan. This series is limited by its small sample size and homogeneous population in a country with a low baseline prevalence of AH and/or EC. Likewise, Tohma et al. (9) investigated the prevalence of AH and/or EC in women seen for an infertility evaluation in Turkey. In their study, 5,560 patients underwent endometrial biopsy or hysteroscopy based on symptoms or ultrasound findings, and 10 (0.18%) were diagnosed with EC and 17 (0.3%) were diagnosed with AH. Although this is the highest prevalence reported in the literature for a reproductive age group, these data only reflect the prevalence of AH and EC within the subpopulation of infertility patients with symptoms or imaging

TABLE 4

Stratified analysis of risk factors.

	Normal weight (BMI <30 kg/m^2)			Obese (BMI ≥30 kg/m^2)			No ovulatory dysfunction			Ovulatory dysfunction		
Risk factor	AOR[a]	95% CI	*P* value	AOR[a]	95% CI	*P* value	AOR[a]	95% CI	*P* value	AOR[a]	95% CI	*P* value
BMI ≥30 kg/m^2	—	—	—	—	—	—	3.11	0.80–12.18	.103	23.30	2.32–233.97	.007
Ovulatory dysfunction	0.68	0.07– 7.01	.747	7.25	1.64– 32.13	.009	—	—	—	—	—	—
African American race	[b]			0.87	0.25– 2.99	.821	0.55	0.10–3.07	.497	0.90	0.18– 4.49	.894
Age	1.06	0.87– 1.29	.557	1.09	0.96–1.24	.204	1.07	0.92–1.24	.404	1.09	0.94–1.28	.261

[a] After adjusting for remaining covariates (age, African American race, BMI ≥30 kg/m^2, ovulatory dysfunction). AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval.
[b] There are no African American cases in the normal weight group, therefore race was dropped from this model.

Kahn. Endometrial cancer risk in patients with infertility. Fertil Steril Rep 2020.

that prompted endometrial sampling rather than all patients presenting for an infertility evaluation. Given that not all patients in our infertility population received endometrial sampling, we are unable to comment on prevalence of disease in the entire infertile population. A strength of the present study is its inclusion of an unrestricted sample of patients with female infertility, therefore allowing calculation of baseline AH and/or EC incidence and quantification of risk factors in an otherwise asymptomatic cohort. The study is further strengthened by the racial diversity of the infertility population, thus increasing generalizability of the results to the American population at large.

Although the high incidence of AH and/or EC in the present study may be due to over-representation of obesity and ovulatory dysfunction in the infertile population, investigational bias may also play a role (8). Outside of an infertility evaluation, it is rare for a young, asymptomatic, patient to undergo uterine cavity assessment or endometrial sampling. In an infertility evaluation, detailed uterine cavity assessment is routine, although endometrial sampling is only performed in the setting of focal findings or symptoms (10). Current best practice guidelines recommend endometrial sampling for patients aged 19–45 years with abnormal uterine bleeding and exposure to unopposed estrogen. Patients >45 years old should be sampled for abnormal uterine bleeding alone (11). Accordingly, the 45% of cases in our study who did not report abnormal uterine bleeding would have experienced a delayed diagnosis without an infertility evaluation. There are currently no recommendations for endometrial sampling in asymptomatic patients with other risk factors and further research is needed to determine the utility of risk-based screening in this population.

The retrospective design of this study carries other inherent biases and limitations. There is potential for a type II error given our small sample size. It is also possible that the true incidence of AH and/or EC in patients undergoing routine infertility evaluation was overestimated or underestimated due to inaccurate coding within the electronic medical record. Some patients had incomplete information within the electronic medical record, particularly when infertility evaluation was started at our institution but not continued. Last, the case-control study design does not enable us to assess change in incidence of AH and/or EC over time.

In summary, the present study found a 10-fold increase in the incidence of AH and/or EC among women undergoing routine infertility evaluation compared with aged women in the general population. Unsurprisingly, obesity was identified as the strongest risk factor for AH and/or EC within this population with infertility. Our data would suggest that physicians should maintain an index of suspicion for AH and EC in even a younger patient with infertility who presents with obesity and/or ovulatory dysfunction. Prospective studies are needed, however, to determine whether selective endometrial sampling based on obesity alone would increase detection of early endometrial pathology in the population of women undergoing an infertility evaluation.

REFERENCES

1. CDC. USCS Data Visualizations—CDC, Available from: https://gis.cdc.gov/Cancer/USCS/DataViz.html. Accessed January 27, 2020.
2. Henley JS, Miller JW, Dowling NF, Benard VB, Richardson LC. Uterine cancer incidence and mortality—United States, 1999–2016. Morb Mortal Wkly Rep 2018;67:1333–8.
3. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, et al. Incidence of endometrial hyperplasia. Am J Obstet Gynecol 2009;200:678.e1–6.
4. Yang HP, Cook LS, Weiderpass E, Adami HO, Anderson KE, Cai H, et al. Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). Br J Cancer 2015;112:925–33.
5. Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. Fertil Steril 2011;95:2690–2.
6. Rackow BW, Arici A. Endometrial cancer and fertility. Curr Opin Obstet Gynecol 2006;18:245–52.
7. Koskas M, Azria E, Walker F, Luton D, Madelenat P, Yazbeck C. Progestin treatment of atypical hyperplasia and well-differentiated adenocarcinoma of the endometrium to preserve fertility. Anticancer Res 2012;32:1037–43.
8. Fujiwara H, Ogawa S, Motoyama M, Takei Y, MacHida S, Taneichi A, et al. Frequency and characteristics of endometrial carcinoma and atypical hyperplasia detected on routine infertility investigations in young women: a report of six cases. Hum Reprod 2009;24:1045–50.
9. Tohma YA, Zeyneloglu HB, Aslan OD, Haberal AN, Onalan G, Ayhan A. Prevalence of endometrial cancer or atypical hyperplasia diagnosed incidentally in infertility clinic. Am J Obstet Gynecol 2018;219:503–5.
10. Practice Bulletin No. 149: endometrial cancer. Obstet Gynecol 2015;125:1006–26.
11. Committee on Practice Bulletins—Gynecology. Practice bulletin no. 136: management of abnormal uterine bleeding associated with ovulatory dysfunction. Obstet Gynecol 2013;122:176–85.