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Fertility preservation and oncological outcomes – a retrospective observational pilot study at a university health institution

Очување плодности и онколошки исходи – ретроспективна опсервациона пилот-студија у универзитетској здравственој установи

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SUMMARY

Introduction/Objective Atypical endometrial hyperplasia (AEH) and endometrial intraepithelial neoplasia (EIN) are precursor lesions endometrioid adenocarcinoma, often detected at an early stage in reproductive-aged women, where fertility-sparing treatment (FST) is crucial. This study aimed to evaluate diagnostic methods, treatment strategies, and outcomes of FST approaches in Novi Sad, Serbia.

Methods This retrospective observational pilot study evaluated reproductive-aged patients with AEH or FIGO IA1 EIN treated at the University Clinical Center of Vojvodina (UKCV).

Results A total of 21 reproductive-aged patients (mean age 37.2 ± 4.31 years) were analyzed, with AEH being the most common diagnosis 14 (67%). Most patients 19 (90%) were referred for oncofertility consultation ($p < 0.001$) and 17 patients (81%) were recommended fertility-preserving treatments. The IUS Mirena was the most common treatment modality 14 (67%) ($p < 0.001$), especially among those planning future pregnancies 11 (100%) ($p < 0.05$). Psychological counseling was considered important by 14 patients (67%). Seven patients (33%) achieved pregnancy post-treatment, all resulting in live births, with four spontaneous and three IVF pregnancies. Younger patients were more likely to plan future pregnancies (mean age 34.2 vs. 40.0 years, $p < 0.001$) and to achieve pregnancy post-treatment (mean age 33.6 vs. 39.1 years, $p < 0.001$).

Conclusion Our study confirmed fertility-preserving treatment for endometrial lesions is effective, aligns with guidelines, and addresses the shift toward younger patients, highlighting the need for uniform protocols and a unified registry.

Keywords: endometrial hyperplasia; endometrial neoplasms; fertility preservation; pregnancy; pregnancy rate

САЖЕТАК

Увод/Циљ Атипична хиперплазија ендометријума (АХЕ) и интраепителна неоплазија ендометријума (ИНЕ) су прекурзорне лезије ендометриоидног аденокарцинома, које се често откривају у раној фази код жена у репродуктивном добу, где је очување плодности од кључног значаја. Ова студија има за циљ да оцени дијагностичке методе, стратегије лечења и исходе приступа очувања плодности у Новом Саду, Србија.

Методе Ова ретроспективна опсервациона пилот студија је укључила болеснице у репродуктивном добу са АХЕ или ИНЕ *FIGO* IA1 стадијума, леченим у Универзитетском клиничком центру Војводине.

Резултати Анализирана је 21 болесница у репродуктивном добу (просечна старост 37,2 ± 4,31 године), при чему је најчешћа дијагноза АХЕ била код 14 (67%) болесница. Већина болесница, 19 (90%), је упућена на онкофертилно саветовање ($p < 0,001$), а 17 болесница (81%) је препоручен третман за очување плодности. Интраутерини систем Мирена био је најчешћи модалитет лечења 14 (67%) ($p < 0,001$), посебно код оних које планирају будућу трудноћу 11 (100%) ($p < 0,05$). Психолошко саветовање је код 14 болесница (67%) сматрало важним. Седам болесница (33%) је остварило трудноћу након лечења, а све су резултирале живим рођењем, од чега четири спонтане и три трудноће помоћу ИВФ. Млађе болеснице су чешће планирале будућу трудноћу (просечна старост 34,2 наспрам 40 година, $p < 0,001$) и остариле трудноћу након лечења (просечна старост 33,6 наспрам 39,1 године, $p < 0,001$).

Закључак Наша студија потврдила је да је третман очувања плодности код лезија ендометријума ефикасан, у складу са препорукама и одговара на тренд раста учесталости код млађих болесница, што истиче потребу за уједињеним протоколима и централним регистром.

Кључне речи: ендометријална хиперплазија; ендометријалне неоплазме; очување плодности; трудноћа; стопа трудноће

INTRODUCTION

Atypical endometrial hyperplasia (AEH), or endometrial intraepithelial neoplasia (EIN), is a precursor to endometrioid endometrial carcinoma (EEC), the most common gynecological malignancy in developed countries [1]. It results from unopposed estrogen stimulation and is associated with obesity, chronic anovulation, early menarche, late menopause, or estrogen-

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secreting tumors. AEH causes abnormal gland-to-stroma proliferation with atypical cellular features and, if untreated, can progress to EC [2, 3].

Endometrial carcinoma (EC), which accounted for 420 368 cases globally in 2022, represents 4.5% of all female cancers. Its incidence has risen by 130% in the last 30 years, with the highest rates in North America and Eastern Europe [4]. Although most cases occur in women over 50, incidents in younger women, especially those with obesity or smoking, are increasing. Around 4% of cases affect women under 40, prompting a growing interest in fertility preservation due to early-stage diagnosis and good prognosis. Fertility-sparing treatment (FST) are becoming more common [5–8]. The traditional treatment for EEC typically involves hysterectomy with or without salpingo-oophorectomy [7]. However, for young patients with early-stage endometrial cancer who wish to preserve fertility, several FST approaches can be considered. When evaluating the possibility of a FST approach, the following criteria must be met: the cancer must be EEC G1, and the disease must be confined to the endometrium, confirmed by imaging diagnostics such as pelvic MRI or transvaginal ultrasound [9, 10]. Additionally, there must be no evidence of suspicious or metastatic disease on imaging, and there should be no contraindications for medical therapy. Patients must also be well-informed that FST is not the standard therapy for endometrial cancer. FST approaches are not recommended for patients with poorly differentiated EEC, serous EC, clear cell EC, or carcinosarcoma [10].

The aim of this study was to present and analyze the current practices in diagnosing and treating premalignant and malignant endometrial changes in reproductive-age women wishing to preserve fertility in Novi Sad, Serbia. It also aimed to comprehensively analyze oncological and reproductive outcomes, including the use of assisted reproductive technologies, and to assess the adequacy of the existing treatment approach in line with recommendations from relevant bodies. The study emphasizes the need for a uniform approach to the issue and proposes recommendations for diagnosis and treatment tailored to the specifics of our healthcare system to optimize both oncological and reproductive outcomes.

METHODS

The study was conducted as a retrospective pilot clinical investigation, utilizing data extracted from medical records and relevant anamnesis information at the Clinic of Gynecology and Obstetrics, University Clinical Center of Vojvodina (UKCV). This included patients with a primary diagnosis of the conditions made at other healthcare institutions, provided they had undergone appropriate pathological verification.

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Patients and data collection

The research included a cohort of 21 patients treated between January 2017 and May 2023, all diagnosed with pathologically confirmed EC and corresponding premalignant lesions, with the common goal of fertility preservation. As this was a retrospective pilot study aiming to explore feasibility and trends in fertility-preserving management, a formal sample size calculation was not performed; all eligible cases treated at the institution during the study period were included to maximize data capture and generate preliminary insights. Inclusion criteria required histopathological confirmation of diagnosis, availability of complete medical records, and a documented decision-making process regarding FST. Pathological confirmation was achieved through histological analysis of endometrial biopsy specimens. The study was conducted in three phases: during the first phase, data relevant to the research objectives were collected from medical records and patient histories; in the second phase, the collected data were subjected to statistical analysis; and in the third phase, the results were compared against current expert guidelines. These guidelines included those of the European Society of Human Reproduction and Embryology (ESHRE), the European Society of Gynecological Oncology (ESGO), and the European Society for Gynecological Endoscopy (ESGE), with the goal of generating tailored recommendations suitable for the context of our healthcare system. A simple flow diagram was added to illustrate patient selection, diagnostic approaches, treatment modalities, and reproductive outcomes in the cohort (Figure 1).

Upon completion of the study, the data were thoroughly verified by the authors, coded for analysis, and entered into a specially designed database. The study results were subsequently presented both in tabular and graphical formats for clearer interpretation and presentation.

Statistical analysis

Statistical analysis was conducted using SPSS® 26.0 software (SPSS Inc., Chicago, Illinois). Descriptive statistics were employed to calculate absolute frequencies, corresponding percentages, mean values (M), and standard deviations (SD), based on the nature of the variables. To assess differences, the Mann-Whitney U test was used for comparing mean values of ordinal variables, while the Chi-square test was applied to evaluate differences between categorical variables. A p-value below 0.05 was interpreted as statistically significant. Data analysis and visualization were performed using Microsoft Office 2021.

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Ethics: The research was performed in line with the Declaration of Helsinki and was approved by the UKCV Ethics Committee (Document No 6-00-97, May 19, 2023)

RESULTS

The sample consisted of 21 patients (with no missing data), with a mean age of 37.2 ± 4.31 years, ranging from 29 to 43 years. Table 1 shows the frequency of patients according to the pathological findings, with AEH being statistically significantly more common. Out of 21 patients, 14 had AEH, 4 had EEC G1, and 3 had EEC G2.

An analysis of the data shows that in 12 patients, the pathological findings were obtained through cervical dilation and curettage (D/C), while in 9 patients, the findings were obtained via hysteroscopy (HSC). Although there is a difference in frequencies, it is not statistically significant ($p=0.664$), indicating a relatively uniform distribution.

Looking at the data in Table 2, it is evident that the majority of patients had already fulfilled the role of a mother prior to diagnosis. The highest number of patients, 19, responded affirmatively to the second question, indicating they were referred to an oncofertility consultation after the diagnosis, and this difference was statistically significant ($p<0.001$). Although no statistically significant differences were found in the remaining binary questions, it is important to note that FST for uterine preservation was recommended to the majority of patients. More than half of the patients believed that psychological counseling was essential in making decisions about further treatment. Nearly the same number of patients answered both "yes" and "no" when asked about planning pregnancy after treatment. Of the total number of patients, only 7 achieved pregnancy after oncological treatment, but all pregnancies resulted in live births.

The majority of patients, 14 in total, were treated with the IUS–Mirena. Oral progestins were recommended for 2 patients, while surgery was proposed as the therapeutic modality for 4 patients. As shown, Mirena is a statistically significantly more common choice compared to other options, with this difference being statistically significant ($\chi^2 = 24.5$, $p < 0.001$).

After treatment, among the seven patients who achieved pregnancy, four conceived spontaneously, while three achieved pregnancies through in vitro fertilization (IVF). Regarding the final question from the anamnesis questionnaire—*Was the uterus removed after the achieved pregnancy?*—none of the seven patients who achieved pregnancy had their uterus removed following delivery. An analysis of the association between the applied therapeutic modality and the pathological findings (Table 3) indicates that in cases of AEH, the most common treatment

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involved the use of the IUS Mirena, applied in 11 patients. Surgical treatment was chosen for two patients, and oral progestins were recommended for one patient. In cases with pathological findings indicating EEC G1, the most frequent therapeutic modality was also Mirena, used in three patients, while surgery was performed in one case. For pathological findings consistent with EEC G2, surgery was the treatment of choice for two patients, while oral progestins were used in one case. χ^2 test results show no significant association between the therapeutic modality and the pathological findings. However, due to the small sample size within the categories, this finding should be interpreted with caution.

When analyzing the association between future pregnancy planning and the applied therapy modality (Table 4), it is evident that in the group of patients planning pregnancy, the IUS Mirena was exclusively used as the therapy of choice, applied in 11 cases. Patients treated with medications and/or surgery did not plan pregnancies. According to the results presented in Table 4, patients with the IUS Mirena were more likely to plan a pregnancy, and this difference is statistically significant ($\chi^2 = 9.90$, $p < 0.05$).

When examining the association between future pregnancy planning and pathological findings, the results indicate no significant difference in future pregnancy planning based on the patients' pathological findings ($\chi^2 = 93.96$, $p < 0.13$).

The results show that patients with an average age of 34.2 ± 3.58 years planned future pregnancies, while those with an average age of 40.0 ± 2.83 years did not. According to the Mann-Whitney U test, there is a significant age difference between patients in relation to future pregnancy planning. Patients who planned future pregnancies were significantly younger than those who did not ($U = 10.00$, $p < 0.001$) (Table 5).

We observe that patients who had live births prior to their diagnosis are more likely not to plan a future pregnancy, and this difference is statistically significant ($\chi^2 = 6.11$, $p<0.01$). There is no significant difference in the frequency of pregnancies following oncological treatment based on the patients' pathological findings ($\chi^2 = 2.20$, $p<0.33$).

According to the results of the Mann-Whitney U test, there is a significant difference in patient age concerning the occurrence of pregnancy after oncological treatment. Patients who became pregnant following oncological treatment are significantly younger than those who did not ($U = 14.00$, $p < 0.001$) (Table 6).

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DISCUSSION

The selection of patients for FST is critical. Major oncology societies, including the Japan Society of Gynecologic Oncology (JSGO), the ESGO, and the Society of Gynecologic Oncology (SGO), have established criteria for considering FST options in cases of AEH and EEC [11, 12, 13]. They recommend FST for patients with EEC G1 suspected to be confined to the endometrium. The British Gynecological Cancer Society (BGCS) also supports FST for patients with EEC G1 exhibiting superficial myometrial invasion, although for a limited duration [14]. According to joint ESGO, ESHRE, and ESGE guidelines, FST is a viable option for early-stage patients with no metastasis, selected based on comprehensive reproductive potential assessment [13, 14, 15]. These criteria typically apply to patients with AEH or EEC G1 confined to the endometrium, with no myometrial invasion and minimal risk of local invasion or metastatic spread. Recent studies suggest that conservative treatment may be considered on a case-by-case basis for women with early-stage G2 EEC (stage IA) or EEC G2 with minimal myometrial invasion (1–2 mm). These histopathological criteria were previously used to exclude FST [16, 17]. Furthermore, other studies [18, 19, 20] have emphasized the diagnostic challenge in distinguishing AEH from well-differentiated carcinoma, with substantial interobserver variability and frequent underdiagnosis of carcinoma in initial biopsy specimens. Discrepancies between D&C and final hysterectomy pathology are particularly well-documented, often revealing occult carcinoma that was not detected initially. This diagnostic uncertainty can influence treatment decisions and underscores the need for accurate sampling, ideally through hysteroscopically guided biopsy. Additionally, studies [21] highlight the role of molecular profiling (e.g., POLE, p53, MMR status) and histopathologic risk factors such as lymphovascular space invasion (LVSI), deep myometrial invasion, and tumor grade in determining suitability for conservative management. These parameters are increasingly recognized as critical in identifying patients for whom FST approaches may pose unacceptable oncologic risks. Our study did not include molecular or immunohistochemical analysis, limiting the ability to stratify patients based on more refined risk profiles.

In our study, of the 21 patients considered for FST, 14 had histopathological findings indicating AEH, 4 had EEC G1, and 3 had EEC G2, aligning with current guidelines. The selection of candidates for FST should include an assessment of ovarian reserve, anti-Müllerian hormone levels, antral follicle count, FSH levels (on days 2–5), age, and BMI, as well as any factors that could affect the patient's ability to carry a pregnancy. Patients with diminished ovarian reserve may still benefit from FST if they opt for oocyte donation.

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As women increasingly delay childbirth, with the average age for first-time mothers in the EU rising to 29.4 years in 2019, age remains a significant prognostic factor for fertility, including in patients with AEH or EEC. In our study, the average age was 37.2 years, with the youngest patient being 29 and the oldest 43, which exceeds the upper range of typical age data. Recent meta-analyses show that women with EEC under 35 have the highest chance of live birth rate - LBR (30.7%), while those under 40 have a LBR of 23.0% [22].

When examining the relationship between age at diagnosis and plans for future pregnancies, our study found a significant difference: younger patients were more likely to plan for pregnancy ($U=10.00$, $p<0.001$). Similarly, patients who achieved pregnancy after oncological treatment were significantly younger ($U=14.00$, $p<0.001$). However, there was no significant difference in pregnancy plans based on histopathological findings ($x2=93.96$, $p<0.13$), consistent with current literature.

The diagnostic procedures for EC include endometrial biopsy, with several methods used, including pipelle sampling, cervical dilation and curettage (D/C), and hysteroscopically guided biopsy. In our study, 12 patients had histopathological findings from D/C, while 9 had results from hysteroscopy. Despite its limitations, D/C has long been favored for obtaining biopsy samples. Studies have shown that D/C samples less than 50% of the endometrial cavity, with up to 10% of lesions missed, par-ticularly focal abnormalities. Consequently, hysteroscopy is now considered the preferred method for endometrial biopsy [13, 23, 24, 25]. For the past 25 years, hysteroscopy and targeted endometrial biopsy have been considered the standard in EC diagnosis. Depending on local findings, a three-step excision technique may be used, ensuring that the obtained material is extracted without introducing the forceps into the operative channel. In cases of atrophic endometrium, bipolar electrodes and scissors are employed for precise lesion removal. Office resectoscopes may also be used to collect larger tissue samples, including subendometrial tissue. A meta-analysis of 65 studies on hysteroscopy's accuracy in diagnosing EC found a sensitivity of 86.4% and specificity of 99.2% [26]. Another meta-analysis, conducted by European and American researchers, confirmed that hysteroscopically guided biopsy is more accurate than blind biopsy for diagnosing endometrial pathology. Concerns regarding the potential for tumor cell dissemination during hysteroscopy are addressed by studies showing no impact on disease staging or prognosis [27]. Additionally, discrepancies in differentiating atypical hyperplasia from well-differentiated carcinoma, especially when using curettage, are well-documented in the literature.

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As with any retrospective observational study, this research has several inherent limitations. Selection bias may have occurred, as only patients who presented to and were treated at a single tertiary center were included, potentially limiting generalizability. Information bias is also possible due to reliance on existing medical records, which may have been inconsistently documented. To mitigate these issues, we included all eligible patients treated during the study period and used standardized criteria for data extraction. Nevertheless, prospective studies with predefined protocols and multicenter collaboration are needed to validate our findings and reduce potential biases. Lastly, this study did not control for potential confounders such as comorbidities, body mass index (BMI) and hormonal status, all of which may have influenced both treatment selection and reproductive outcomes. Future studies should include a larger, more diverse sample and account for these confounding variables to better identify independent predictors of fertility-preserving treatment success and reproductive outcomes.

CONCLUSION

Our study confirms the effectiveness and safety of FST for premalignant and malignant endometrial lesions, aligned with ESGO, ESHRE, and ESGE guidelines. Younger patients, often without children, increasingly seek preservation, with 4% of cases in women under 40. Hormonal therapy, LNG-IUS, and hysteroscopic resection show good outcomes, while post-remission monitoring, ART, and psychological support are essential. In the absence of large studies, a comprehensive evaluation of health and reproductive potential is key before recommending FST. Our findings highlight the need for a unified registry for monitoring oncofertility and a personalized approach to treatment for each patient.

Conflict of interests: None declared.

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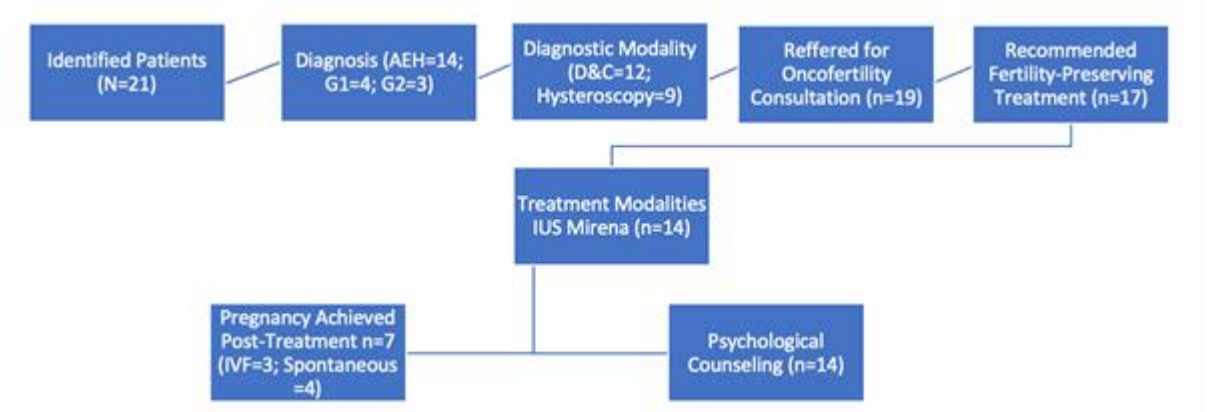

Figure 1. Flow diagram regarding patient selection, diagnostic approaches, treatment modalities, and reproductive outcomes in the cohort

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Table 1. Distribution of patients according to pathological findings

Pathohistological-cal findings	N (%)	p
AEH	14 (66.7)	0.189
EEC G1	4 (19)	0.007
EEC G2	3 (14.3)	0.001
Total	21 (100)	

AEH – atypical endometrial hyperplasia; EEC – endometrioid endometrial carcinoma

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Table 2. Distribution of patient responses to binary questions from the anamnesis questionnaire

Question answered with 'Yes'	N (%)	p
Do you have living children prior to the diagnosis?	14 (66.7)	0.189[a]
When was your diagnosis made, and were you presented to the oncofertility consultation?	19 (90.5)	**< 0 .001**[a]
If presented to the oncofertility consultation, was fertility-preserving treatment for uterine preservation and further oncological treatment recommended?	17 (81)	0.007[a]
Do you think you should have received psychological counseling before making this decision?	14 (66.7)	0.189[a]
Did you plan pregnancy after completing oncological treatment?	10 (47.6)	1.000[a]
Did you achieve pregnancy after oncological treatment?	7 (33.3)	0.189[a]
Did the pregnancy result in a live birth?	7 (33.3)	0.189[a]
Total	21 (100)	

[a]χ^2 test

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Table 3. The association between pathological findings and the type of prescribed therapy

Therapeutic modalities	Pathohistological findings						
	AEH	EEC G1	EEC G2	Total	χ^2	df	p
Mirena	11	3	0	14	11.2	8	0.08[a]
Medication	1	0	1	2			
Operation	2	1	2	5			
Total	14	4	3	21			

AEH – atypical endometrial hyperplasia; EEC – endometrioid endometrial carcinoma;

[a]χ^2 test

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Table 4. Association between future pregnancy planning and the applied therapy modality

Pregnancy planning	Therapeutic modalities					
	Mirena	Medication	Operation	Total	χ^2	p
Yes	11	0	0	11	9.90	$< 0.05^a$
No	4	2	4	10		
Total	15	2	4	21		

[a]χ^2 test

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Table 5. Differences in future pregnancy planning by age

Pregnancy planning	N	Mean (years)	Median (years)	SD	SE	U	p
Yes	10	34.2	33.5	3.58	1.13	10.00	< 0.001[b]
No	11	40	39	2.83	0.853		

[b]Mann–Whitney U test

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Table 6. Age of patients in relation to the occurrence of pregnancy after oncological treatment

Pregnancy	N	Mean (years)	Median (years)	SD	SE
Yes	7	33.6	33	3.78	1.43
No	14	39.1	39	3.34	0.892

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