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ORIGINAL ARTICE

Hysteroscopic Endometrial Resection and Insertion of Levonorgestrel Intrauterine Device (LNG-IUD) as a Fertility Preserving Procedure in Young Females with Atypical Endometrial Hyperplasia

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ABSTRACT

Background: The conservative management of atypical endometrial hyperplasia (AEH) using different management strategies will be important in females who want to conceive. However, complete data were lacking regarding selection criteria of the patients, optimal therapeutic strategies, and follow-up periods. The aim of this study was to evaluate feasibility, safety, effectiveness, fertility, and long-term outcomes of hysteroscopic endometrial resection in combination with Levonorgestrel Intrauterine Device (LNG-IUD) as fertility-sparing strategies of management of premenopausal young females with AEH. **Methods:** We prospectively evaluated clinical files of 35 patients with AEH who underwent hysteroscopic resection of the lesion with insertion of LNG-IUD. LNG-IUD maintenance in its site was made for 12 months then removal of it was made for women with complete response (CR) then they were allowed to conceive naturally. Patients with recurrent, progressive, or resistant disease will undergo definitive surgical management by total hysterectomy and bilateral salpingoophorectomy. **Results:** We found that about 31 (88.5%) patients achieved and maintained a CR and LNG-IUD removed. 20 out of the 31 patients (64.5%) who had removed LNG-IUD became pregnant after natural conception in the following twelve months. 13 (65%) babies were born by Caesarean section at 39 weeks of gestation, and seven (35%) were born at term spontaneously. We found no recurrence in the 24 months of follow-up. **Conclusions:** We showed that combination of hysteroscopic superficial endometrial resection followed by insertion of LNG-IUD was considered safe and effective management procedure for young females with AEH who desired to preserve their fertility due to negligible progression and recurrence rates with accepted pregnancy and life births rates. **Keywords:** Atypical endometrial hyperplasia, Fertility sparing, Hysteroscopic resection, LNG-IUD

INTRODUCTION

Endometrial intra-epithelial neoplasia (EIN) with atypia has been considered a premalignant lesion as within few years it progresses to endometrial carcinoma (EC) in about 30% of cases [1]. EC is the commonest gynaecologic malignancy in Western countries and its incidence was rabidly increasing in Eastern countries [2]. The standard treatment for women diagnosed with atypical endometrial hyperplasia or EC is a total hysterectomy with bilateral salpingo-oophorectomy. Although most cases were diagnosed after menopause, EIN and EC were diagnosed in a large number of premenopausal young nulliparous women who need to get pregnant [3], so it will be important to provide fertility-sparing treatment options for EIN to them in addition to informing them about the radical treatment options.

Fertility-sparing treatment was primarily showed by Kistner [4] where he described successful treatment of 7 cases of EIN with progestins without the need for radical management and one patient in his report got pregnant. A hysteroscopic resection of diseased endometrium in combination with GnRH

agonist was described by Jadoul and Donnez demonstrated in 2003 as a fertility sparing technique which provided good feasibility, fertility, and safety [5].

Recently systemic medical treatment using oral progestins in high doses or levonorgestrel-releasing intra-uterine device (LNG-IUD), gonadotropin-releasing hormone agonist, oral contraceptives, letrozole and tamoxifen in addition to surgical resection of the lesion were considered the currently used fertility sparing strategies of management of EIN or early-stage EC [3, 6, 7].

It was previously described that about 10 % of young patients with AEH might have foci of EC or a synchronous cancer [8], so a hysteroscopic uterine and abdominal exploration with resection and biopsies from any suspicious lesion from the endometrium or ovaries under direct vision should be done to exclude uterine cancer and extra-uterine disease [9].

The conservative management of EH using different management strategies will be important in females who want to conceive. However, complete data were lacking regarding selection criteria of the patients, optimal therapeutic strategies, and follow-up periods.

The aim of this study was to evaluate feasibility, safety, effectiveness, fertility, and long-term outcomes of hysteroscopic endometrial resection in combination with LNG-IUD as fertility-sparing strategies of management of premenopausal young females with AEH.

METHODS

We prospectively evaluated clinical files of 35 patients with AEH treated in Obstetrics and Gynaecology Department, Faculty of Medicine, Zagazig University in the period between March 2012 and December 2017. We collected forty patients aged 20–40 years (mean age was 33.5 years) diagnosed with AEH who wanted to preserve their fertility. About 35 patients had AEH without EC; we excluded 3 patients with EC and 2 patients with both EC and AEH as they underwent definitive surgery. Inclusion criteria were nulliparous patients between 20 and 40 years with a sure diagnosis of AEH who desired to conceive and preserve their fertility regardless informed liability of malignant transformation or oncological risk, while females older than 45 years with a sure diagnosis of EC with uterine infiltration and patients with extrauterine spread or synchronous malignancy were excluded. Cases with post-operative intra uterine synechiae, cases with preterm labour and cases with placental abnormalities were also excluded from the study. In addition, cases with fetal or maternal problems were excluded from the study because these points were away from our main point of research which is recurrence free and survival free rates.

We have informed the 35 patients included in the study that fertility-sparing management was not the standard one and that the gold standard for their condition was hysterectomy. Hysteroscopy assisted endometrial diagnostic biopsy was carried out. We found thickened irregular endometrium with focal polypoid areas which made us suspect the possible presence of Endometrial hyperplasia with atypia.

The designed fertility-sparing management strategies in our study: First we performed hysteroscopic resection of the grossly apparent exophytic lesions (specimen 1), second, we removed muscle layer below the lesion (specimen 2), and third we removed endometrium away from the lesion by about 5-6 mm superficially and preserving the basal layer (specimen 3). Then we obtained multiple random endometrial biopsies leaving the basal layer. In case of confirmation of EC in any specimen; the patient was excluded. In patients with histological confirmation of AEH in specimen 1 with free specimen 2 and 3 we considered for hysteroscopic resection as a definitive management, and we inserted the LNG-IUD. All hysteroscopic operative procedures were performed by expert gynaecologic surgeons under loco-regional or general anaesthesia.

We acquired a confidential letter from the head of endoscopic unit and the head of the department proving performing this study. The cervix was dilated by Hegar's dilator to 10 mm then introduction of a 26-27 Fr bipolar resectoscope with 0°-12° lens was done. Distention of the uterus with normal saline was done then a cutting loop electrode of 4-5-mm was used.

Assessment of therapy outcomes: We classified oncologic outcomes into; complete response (CR) which was defined by absence of any pre-management disease, partial response (PR) which was defined as AEH regression to hyperplasia without atypia, stable disease (SD) which was defined as pre-management disease persistence and progression (P) which means progression of AEH to EC. We considered occurrence of AEH after CR as relapse (R).

LNG-IUD maintenance in its site was made for 12 months then removal of it was made for women with CR then they were allowed to conceive naturally. Assessment of the reproductive outcome was made by successful pregnancy occurrence and outcomes which were subdivided into full term or preterm by gestational age, additionally adequate monitoring to patients was performed to detect abnormal placental conditions in pregnant women. Patients with recurrent, progressive or resistant disease will undergo definitive surgical management by total hysterectomy and bilateral salpingoophorectomy.

Patients with complete absence of the disease who achieved CR were monitored carefully, allowed to conceive, and underwent diagnostic hysteroscopic endometrial biopsy every 3 months until occurrence of pregnancy. After pregnancy and delivery, hysteroscopic endometrial sampling was performed every 3 months until a second pregnancy occurred. If recurrence of the disease or progression occurred at any time or the patients completed their families or become old to get pregnant definitive surgery was performed.

Written informed consent was obtained from all included patients, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis was done by using Statistical Package for the Social Sciences (SPSS) statistical software (version 23.0; SPSS Inc, Chicago, IL). Mann-Whitney U tests was used to compare between continuous variables. Pearson's $\chi 2$ and Fisher's exact tests were used for comparing between categorical variables. Survival curves were performed analysed and compared using Kaplan-Meier method and log-rank test. P value of $p<0.05$ was considered statistically significant.

RESULTS

Out of the 35 included AEH patients, 31 (88.5%) achieved a CR, 1 (2.8%) had subsequent R, 2 (5.7%) showed PR, while 1 (2.8%) had SD **(Table 1, Figure 1)**. Reproductive outcomes are shown in **Table 2**. The 31 patients who had achieved and maintained CR had LNG-IUD removed.

Among the 31 patients who had removed LNG-IUD, 20 patients (64.5%) became pregnant after natural conception in the following twelve months. 13 (65%) babies were born by caesarean section at 39 weeks of gestation, and seven (35%) were born at term spontaneously. No placental abnormalities or pregnancy and delivery complications occurred. We found no recurrence in the 24 months of follow-up **(Table 3)**.

Table 1: Demographic and clinical data of included patients

	AEH N=35
Age (years):	
Mean ± SD	**33.3 ± 8.18**
Range	**20 - 40**
Parity:	
Nulliparous	**35 (100%)**
BMI:	**32 [20–48]**
Smoking:	
Absent	**30 (85.7%)**
Present	**5 (14.3%)**
Familial cancer:	
Present	**20 (57%)**
Absent	**15 (43%)**
Symptoms:	
Absent	**15 (43%)**
Pain	**10 (28.5%)**
Bleeding	**10 (28.5%)**

	AEH N=35
Previous abdominal Surgery:	
Present	**11 (31.4%)**
Absent	**24 (68.6%)**
History of primary infertility	
Present	**15 (43%)**
Absent	**20 (57%)**
Comorbid Medical Problems:	
Present	**13 (37%)**
Absent	**22 (62.9%)**

Table 2: Reproductive outcome of included patients

Women who maintained complete response at 24 months (N=31)	Histological diagnosis	AEH
	Mirena removed to attempt to conceive	N=22 (%)
Women who attempted to conceive during follow-up (N=31)	Histological diagnosis	AEH
	Conception achieved	Yes=20 (64.5%) No=11 35.5%)
Pregnancies (N=20)	Conception Method	Natural=20 (100%) Assisted=0 (0%)
	Live birth achieved	Yes=20 (100%) No=0 (0%)
	Complications	Yes=0 (0%) No=20 (100%)
	Abnormal Placentation	Yes=0 (0%) No=20 (100%)
Deliveries (N=20)	Delivery Method	Spontaneous vaginal=7 (35%) Cesarean section=13 (65%)
	Delivery Time	Full term=20 (100%) Preterm=0 (0%)
	Complications	Yes=0 (0%) No=20 (100%)

Table 3: Oncological outcome of included patients

Response to treatment:	
PD	**1 (2.8)**
SD	**2 (5.7)**
PR	**1 (2.8)**
CR	**31 (88.5)**
Relapse:	
Absent	**31 (100)**
Present	**0 (0)**
Death	
No	**31 (100)**
Yes	**0(0)**
Disease free survival:	
Median	**14.5 M**
Range	**12 – 22 M**

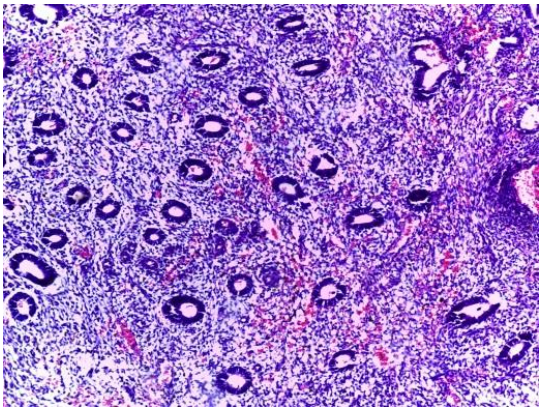

Figure 1A: Simple endometrial hyperplasia without atypia

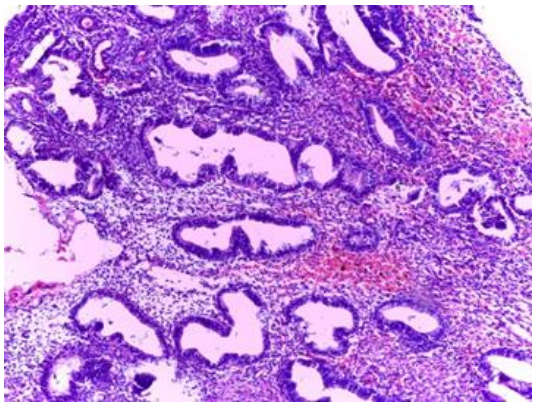

Figure 1B: Endometrial hyperplasia without atypia

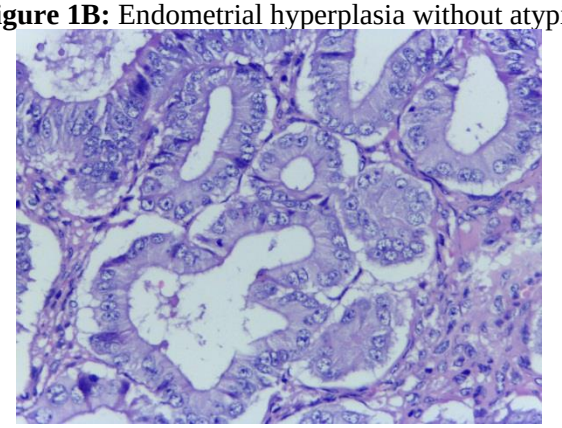

Figure 1C: Endometroid endometrial carcinoma

DISCUSSION

According to results of the present study we showed that combined hysteroscopic endometrial resection followed by insertion of LNG-IUD could be considered safe, feasible and effective fertility-sparing procedure with negligible rates of recurrence or progression in young females with AEH who want to conceive. Our results were near the results of Giampaolino et al., [2] who used the same management fertility preserving procedure in both EC of early stage and in AEH. Our results were similar to the results of former studies which used the same fertility preserving approach [10-13].

Shan et al., [14] showed high CR rate in patients with AEH managed by hysteroscopic endometrial resection followed by megestrol acetate reaching about 83.3%. More recently De Marzi et al., [12] reported a CR rate of 100% in case of patients diagnosed with AEH and managed by hysteroscopic

resection of the hyperplastic areas followed by hormonal therapy.

In our study all patients with AEH underwent hysteroscopic endometrial resection followed by LNG-IUD insertion, as described by Shan et al., [14] and Giampaolino et al., [2]. This technique allows removal of pathologic endometrial tissue and increases the hormonal responsiveness. Moreover, removal of the superficial diseased layer of the endometrium with basal layer preservation allowed a complete endometrial regeneration after finishing the course of hormonal therapy, so preserving females' fertility.

CR rate in our study was higher than those previously reported in females with AEH treated by only oral progesterone alone [15, 16].

Wei et al., [17] in their meta-analysis showed a relapse rate of 20% in females with AEH who were successfully managed by progestins, and the relapse rate was higher in females treated by oral progestins than in those who were treated by intrauterine released progestins.

Yang a et al., [9] showed that fertility preserving management of AEH in young females who want to get pregnant is widely accepted instead of radical surgical management because it could treat the disease successfully in addition to preserving fertility. Using progestin in high doses for a minimum of 6 months is suggested [18].

The liability to disease recurrence and progression to EC in cases of AEH could not be neglected so women underwent the fertility saving management were encouraged to get pregnant as early as possible and definitive surgical treatment is performed once they completed their family or get old to be pregnant [2, 18].

Although hysteroscopy was found to be a safe and effective diagnostic procedure of AEH and EC [19, 20], it was shown in a former study that few cases who underwent hysteroscopic EC resection had recurrence, and all the recurrences were AEH with no cancer recurrence [21].

A recent meta-analysis has compared between the most commonly used fertility preserving management modalities (high dose oral progestin only, levonorgestrel IUD combined with gonadotropin therapy, hysteroscopic resection followed by oral progestin therapy) regarding remission, recurrence, progression, and pregnancy rates. They found that although pregnancy rates were similar in all groups, the best method was hysteroscopic resection followed by IUD insertion while oral progestin alone has the highest recurrence rate [22], and these results strengthens our findings.

Despite the proved benefits of hysteroscopic resection of pathological endometrial tissues in controlling the disease and preserving fertility with lower recurrence rates, there was still a possibility of cancer spread to the peritoneal cavity. So further studies are needed to detect benefits of such procedure and to assess how to avoid cancer spread risks.

Conclusions: We concluded that combination of hysteroscopic superficial endometrial resection followed by insertion of a LNG-IUD for 12 months was considered safe and effective management procedure for young females with AEH who desired to preserve their fertility due to negligible progression and recurrence rates with accepted pregnancy and life births rates.

Strengths of the study: Strengths were the prospective nature of the study which included adequate patients' number and that we restricted the study on only patients with AEH and we have not included EC as previous studies which decreased the selection bias and provided homogenous accurate findings.

Limitations of the study: The relatively short follow-up period and the absence of a control group to compare the results with. We did not evaluate occurrence of post-operative intra uterine synechiae, cases with preterm labour and cases with placental abnormalities, occurrence of fetal or maternal problems because these points were away from our main point of research which is recurrence free and survival free rates. So, larger randomized studies are needed to confirm feasibility, applicability, and safety of using fertility preserving combined treatments with taking into consideration the oncologic and reproductive benefits.

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DECELERATION OF INTEREST

The authors report no conflicts of interest.

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