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Outcomes of *In Vitro* Fertilization in Infertile Patients with Early-Stage Endometrial Cancer or Atypical Endometrial Hyperplasia: An Analysis of 31 Cases

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Abstract

Aim: To assess the effectiveness of intracytoplasmic sperm injection (ICSI) or *in vitro* fertilization (IVF) and embryo transfer (IVF-ET) in infertile patients with early-stage endometrial cancer (EC) or atypical endometrial hyperplasia (AEH).

Methods: Patients with well-differentiated, early-stage EC or AEH who achieved complete reversion of the endometrium after conservative treatment and who underwent IVF-ET between January 2012 and December 2015 were collected. Fertilization rate, implantation rate, pregnancy rate and AEH/EC recurrence rate were measured.

Results: A total of 31 patients were included, of whom 25 (80.65%) had AEH and 6 (19.35%) had well-differentiated early-stage EC. Mean duration of conservative treatment was 8.25 ± 4.08 months, while mean age at entering the IVF cycle was 34.9 ± 3.8 years. The average number of embryos transferred was 1.7 ± 0.8. The IVF and ICSI fertilization rates were 77.6% and 68.2%, respectively. The implantation and pregnancy rates were 29.6% (16/54) and 41.9% (13/31), respectively. There were 13 cases of intrauterine pregnancy with a clinical pregnancy rate of 41.9%. Recurrence of endometrial lesion occurred in 2 (6.45%) patients.

Conclusion: Assisted reproductive technology is a good option in well-selected patients with early-stage EC or AEH who show complete reversion of the endometrial lesion after conservative therapy.

Keywords: Atypical endometrial hyperplasia; Early-stage endometrial cancer; Endometrial reversion; High-dose progestin; IVF-ET

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Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy worldwide, accounting for 6% of all female cancers with a lifetime incidence rate of about 2.5% [1]. Nearly 300,000 women develop EC each year [2], and the incidence of EC has been predicted to increase in both developed and developing countries [3]. Type IIEC (estrogen-independent) typically has non-endometrioid histology and presents, often at an advanced stage, in postmenopausal women. In contrast, type IEC is estrogen-dependent and mainly occurs in women of reproductive age, particularly those with ovulatory disorders, menstrual irregularities, hypertension or diabetes. Furthermore, the observed association between type I EC and atypical endometrial hyperplasia (AEH) had led to the suggestion that AEH may be a precursor of EC [4]. Various molecular mechanisms have been proposed to contribute to the development and progression of EC [5], and it is hoped that further elucidation of these mechanisms will facilitate the development of novel therapies. The current management strategies for EC include hysterectomy, hormonal therapy, radiotherapy and chemotherapy, and the overall survival rate for patients with early-stage EC is nearly 90% [5].

Since type I EC typically occurs in women of reproductive age,

the preservation of fertility is often an important consideration when decisions regarding treatment options are made, particularly since more women are having their first child later in life [6]. Thus, conservative management strategies are utilized in selected patients with EC or AEH in order to maintain future fertility [7-9]. A variety of conservative therapies are available, including high-dose progestin, progestin-releasing intrauterine devices, gonadotropin-releasing hormone agonists (GnRH-a), oral contraceptives and aromatase inhibitors, and their efficacies in premenopausal women with early-stage EC or AEH have been demonstrated by numerous studies [10-16]. Of all these treatments, high-dose progestin is reported as being most frequently used and has good efficacy and safety. For women with no history of infertility who wish to have a child after treatment, spontaneous conception is encouraged right after complete reversion of the endometrium is achieved. For women with chronic anovulation, induction of ovulation with clomiphene citrate (CC), aromatase inhibitors or human menopausal gonadotropins is recommended. For patients who fail to achieve pregnancy with the above treatments, *in vitro* fertilization and embryo transfer (IVF-ET) are recommended to attain pregnancy as soon as possible and before recurrence of the endometrial lesion.

However, the methods used for ovarian stimulation in IVF-ET protocols induce a hyper-estrogenic status that could potentially promote the recurrence of EC. Despite this, only a small number of studies have examined the influence of assisted reproduction techniques (ART) on the recurrence of endometrial lesions or pregnancy outcomes after conservative therapy for EC or AEH. Therefore, the present study retrospectively analyzed the effectiveness of IVF-ET after conservative therapy for EC or AEH in patients at a single institution (Peking Union Medical College Hospital) in China.

Materials and Methods

Patients

Patients treated at the reproductive center of Peking Union Medical College Hospital from January 2012 to December 2015 were enrolled into this retrospective study. Patients were included if they met the following criteria: AEH or well-differentiated early-stage EC was diagnosed by endometrial biopsy; and IVF-ET was received after complete reversion of the endometrium following conservative treatment. Complete reversion of the endometrium after conservative treatment was defined as no evidence of endometrial hyperplasia or EC on pathologic examination. Patients were excluded if EC/AEH was not completely reversed or progressed after conservative therapy. This study was approved by the ethics committee of Peking Union Medical College Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided informed consent for the treatments they received. Due to the retrospective and anonymized nature of the study, consent for inclusion in the study was waived.

Controlled Ovarian Hyper Stimulation (COH)

Short-acting GnRH-a long protocol

Serum FSH, LH, PRL, E2, progesterone, testerone concentrations and β-HCG were measured on day 2 of the last menstrual cycle together with ultrasound exams, and then Marvelon was given. On day 18 of taking Marvelon, GnRH-a (0.1 or 0.05 mg/qd) was added. The ovarian response was monitored through FSH, LH, E2, T and ultrasound exams on day 4 of the next menstrual cycle. GnRH-a was adjusted to 0.05 mg/qd and Gn (150-225 U) was given. When a follicle reached 22 mm, or two follicles reached 20 mm, 250 μg of hCG was administered. Oocytes were retrieved 36 h later. ET was performed 36 h later after oocyte retrieval.

Antagonist protocol

Gn stimulation was initiated on day 2-3 of the menstrual cycle. When objective follicle reached 12-14 mm or LH>10 mIU/ml, GnRH antagonist (Sizekai) was administered 0.25 mg/d until injecting hCG. When a follicle reached 20 mm or two follicles reached 18 mm, 250 μg of hCG was administered. Oocytes were retrieved 36 h later. ET was performed 36 h later after oocyte retrieval.

Long-Acting GnRH-a by Down Regulation Protocol

GnRH-a (1/5 to 1 dosage) was initiated on day 2 of the menstrual cycle, and ovarian response was monitored through FSH, LH, E2, T, P assessments and ultrasound examinations after 20 days. Gn (300 IU/d) was administered when levels of FSH, LH and E2 reached <5 mIU/ml, <3 mIU/ml and 30 pg/ml, respectively. Gn doses were adjusted when needed. When a follicle reached 22 mm, or two follicles reached 20 mm, 250 μg of hCG was administered. Oocytes were retrieved 36 h later. ET was performed 36 h later after oocyte retrieval.

IVF and ET

The oocytes were inseminated approximately 4 to 6 hours after follicular aspiration by a conventional method of IVF or intracytoplasmic sperm injection (ICSI) depending on the semen parameters. Morphologic criteria were used for embryo scoring. On day 3, two high-quality embryos were picked out for fresh transferor cryopreserved by means of vitrification in the group undergoing frozen embryo transfer.

Clinical data collection

The following baseline information was extracted from the medical records: age; body mass index (BMI); age at menarche; menstrual regularity (regular or irregular); duration of infertility; type of infertility (primary or secondary); cause of infertility; parity; family history of diabetes or hypertension; presence of any comorbidities; type of endometrial disease (AEH or EC); conservative treatment used; duration of conservative treatment; and age at entering IVF/ICSI therapy.

Outcome measures

The IVF/ICSI cycle characteristics assessed were number of oocytes retrieved, number of metaphase-II (MII) oocytes, number of embryos transferred and insemination rate. The following IVF/ICSI-ET outcome measures were analyzed: IVF fertilization rate, ICSI fertilization rate, implantation rate and clinical pregnancy rate. Clinical pregnancy was defined as the presence of a gestational sac in the uterine cavity at 35 days after embryo transfer, as detected on ultrasonography.

Statistical analysis

The data were analyzed using descriptive statistics. Quantitative data are expressed as the mean ± standard deviation (SD) or median (range). Enumeration data are expressed as n(%). All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics of the patients included in the analysis

A total of 31 patients (age, 34.9 ± 3.8 years; BMI, 25.8 ± 4.2 kg/m^2) were enrolled in this study; their baseline clinical characteristics are shown in **Table 1**. Among these 31 patients, 25 (80.65%) had AEH and 6 (19.35%) had well-differentiated, early-stage EC. None of the patients diagnosed with EC showed any evidence of myometrial invasion or extra-uterine metastasis on pelvic magnetic resonance imaging. Among the 31 patients, 21 (67.74%) had a history of irregular menstruation, 1 (3.23%) had previously given birth, 7(22.58%) had a family history of hypertension, 5 (13.51%) had a family history of diabetes mellitus, 6 (19.35%) had hysteromyoma and 1 (3.23%) had ovarian cysts. The duration of infertility was 5.53 ± 4.42 years, with primary infertility the underlying cause in 24 (77.42%) patients. The possible causes of infertility included disorders of ovulation, fallopian tube obstruction, endometrial lesions and male factors. The most commonly used conservative treatment was progestin (25/31, 80.65%), followed by progestin combined with GnRH (2/31, 6.45%), progesterone contraceptive ring combined with GnRH (2/31, 6.45%), GnRH combined with ovulation induction (1/31, 3.22%) and progestin+ GnRH + ovulation induction (1/31, 3.23%). The mean duration of conservative treatment was 8.25 ± 4.08 months, while the mean age at entering the IVF cyclewas 34.9 ± 3.8 years.

IVF cycle characteristics

Among the patients achieving complete reversion of the endometrium after conservative treatment, 11 (35.5%) received IVF/ICSI-ET within 2 years while the remainder underwent IVF/ICSI-ET 3 to 12 years after the reversion. The COH protocols included [17] long-acting GnRh-a long protocol, 7 short-acting GnRh-a long protocol and 7 antagonist protocol. Information regarding the IVF cycle characteristics is summarized in **Table 2**. The average number of retrieved oocytes was 6.0 ± 4.0, while the average number of MII oocytes was 5.1 ± 4.1. The average number of embryos transferred was 1.7 ± 0.8, and the insemination rate was 83.9% for IVF and 16.1% for ICSI.

Table 1 Baseline clinical characteristics of the patients included in the analysis.

Characteristics	Value (n=31)
Age (years)	34.9 ± 3.8
Body mass index (kg/m^2)	25.8 ± 4.2
Age at menarche (years)	13.1 ± 1.2
Irregular menstruation, n (%)	
Yes	21 (67.74%)
No	10 (32.26%)
Duration of infertility (years)	5.5 ± 4.4
Type of infertility, n (%)	
Primary infertility	24 (77.42%)
Secondary infertility	7 (22.58%)
Cause of infertility, n (%)	
Male factor	14 (45.16%)
Endometrial lesions	28 (90.32%)
Fallopian tube abmormality	5 (16.13%)
Failure of ovulation	24 (77.43%)
Childbearing history, n (%)	
Yes	1 (3.23%)
No	30 (96.77%)
Family history, n (%)	
Hypertension	7 (22.58%)
Diabetes	5 (13.51%)
None	19 (61.29%)
Complications, n (%)	
Hysteromyoma	6 (19.35%)
Ovarian cysts	1 (3.23%)
Hypertension	2 (6.45%)
Diabetes	2 (6.45%)
None	20 (64.51%)
Type of disease, n (%)	
Moderate or severe atypical endometrial hyperplasia	25 (80.65%)
Well-differentiated, early-stage endometrial cancer	6 (19.35%)
Conservative treatment, n (%)	
Progestin	25 (80.65%)
Progestin + GnRH	2 (6.45%)
Progesterone contraceptive ring + GnRH	2 (6.45%)
GnRH + ovulation induction	1 (3.22%)
Progestin + GnRH + ovulation induction	1 (3.22%)
Duration of conservative treatment (months)	8.25 ± 4.08
GnRH, gonadotropin-releasing hormone	-

Table 2 IVF cycle characteristics of 31 women given conservative treatment for endometrial lesions.

Cycle characteristic (31 cycles)	Value
Average number of oocytes retrieved	6.0 ± 4.0
MII oocytes	5.1 ± 4.1
Number of embryos transferred	1.7 ± 0.8
Insemination, %	83.90%
ICSI	16.10%
ICSI: Intracytoplasmic Sperm Injection; IVF: *In Vitro* Fertilization; MII: Metaphase-II; SD: Standard Deviation.	

Clinical outcomes

Table 3 compares the IVF/ICSI-ET outcomes of the 31 women included in this study (31 cycles) with general data from our center (4090 cycles) during the same period of time. The IVF and ICSI fertilization rates of the 31 patients included in this study were 77.6% and 68.2%, respectively, compared with overall values of 76.2% and 87.8% in our center during the same time period. The implantation and pregnancy rates of the 31 patients were 29.6% (16/54) and 41.9% (13/31) respectively, numerically slightly lower than values of 31.9% and 51.2%, respectively, in our center during the same time period. There were 13 (41.9%) cases of clinical pregnancy, among whom 8 cases had already delivered a singleton healthy baby and 3 cases had already delivered twins by the time of the analysis with the live birth rate of 35.5% (11/31). While embryo damage was happened in the other 2 cases.

Case Reports

Only 2 (6.45%) of the 31 patients who underwent IVF-ET experienced recurrence of endometrial malignancy; these cases are briefly described below.

Case 1

A 43-year-old woman with an 18-year history of primary infertility and AEH who achieved complete reversion of the endometrium after conservative therapy. The patient then underwent a total of three cycles of COH and three cycles of frozen-thawed embryo transfer. However, this patient experienced two recurrences of an endometrial lesion during COH that were diagnosed by pathologic examination as AEH and EC with local myometrial invasion, respectively. Radical surgical therapy with total hysterectomy, bilateral salpingo-oophorectomy and retroperitoneal lymph node assessment was performed, and the pathologic analysis revealed a grade I, well-differentiated endometrioid carcinoma.

Case 2

A 32-year- old woman with a 1-year history of primary infertility and EC who achieved complete reversion of the endometrium after high-dose progestin therapy. The patient underwent two cycles of COH and two cycles of frozen-thawed embryo transfer from 2013 to 2014. A pathologic examination before the third cycle of COH revealed AEH. Oral megestrol acetate was prescribed and complete reversion was achieved again. The patient decided not to continue with IVF-ET due to endometrial damage after dilation and curettage (D&C), and it was recommended that she received progestin treatment for 2 weeks every month in order to protect the endometrium.

Table 3 Comparison of IVF-ET outcomes between the 31 women in the study and general data for our center during the same period of time.

Outcome	31 patients (n=31 cycles)	General data (n=4090 cycles)
IVF fertilization rate (%)	77.6	76.2
ICSI fertilization rate (%)	68.2	87.8
Implantation rate (%)	22.2	31.9
Pregnancy rate (%)	39.3	51.2

ICSI: Intracytoplasmic Sperm Injection; IVF: *In Vitro* Fertilization.

Discussion

The main finding of this study was that IVF/ICSI-ET was successfully used to achieve clinical pregnancy rate of 41.9% (13/31) in patients with AEH or well-differentiated, early-stage EC who showed complete reversion of the endometrium after conservative therapy. Notably, the IVF fertilization rate, ICSI fertilization rate, implantation rate and pregnancy rate in these 31 patients were similar or only moderately lower than general values for our center during the same time period. Furthermore, recurrence of endometrial malignancy occurred in only 2 of the 31 patients. These data support the use of ART in well-selected patients with early-stage EC or AEH who show complete reversion of the endometrial lesion after conservative therapy.

Surgical therapy, including hysterectomy, is an important management strategy for AEH and EC. However, approximately 5% of all cases are diagnosed in women younger than 40 years old, and hysterectomy may not be an acceptable therapy for younger women if they wish to preserve their fertility [17]. High-dose progestin therapy, the most commonly used of these methods, is considered to be a safe and effective option in patients who want to preserve their fertility [18-21]. High-dose progestin was the most frequently used therapy in our study, consistent with a systematic review of 45 previous reports 15. However, there is still no commonly accepted consensus regarding the optimal treatment protocol. For women who temporarily do not wish to conceive after the initial reversion, maintenance therapy with cyclic progestin, oral contraceptives or a progestin-containing intrauterine device is reasonable, and these patients should still be followed with periodic pelvic ultrasound and/or D and C [21].

A successful pregnancy is not always achieved after conservative treatment of EC or AEH with high-dose progestin. Indeed, only a few cases of successful spontaneous pregnancy have been reported after conservative therapy [22]. ART is considered an effective technique for achieving pregnancy after conservative treatment of endometrial lesions in infertile patients with severe ovulatory disorders, fallopian tube obstruction and/or oligospermatism. Thus, IVF-ET is recommended to patients who fail to achieve a natural pregnancy [23]. A recent systematic review 11 of 451 women treated conservatively for early-stage EC or AEH found that the live birth rate was 39.4% (56/142) in women given ART compared with a value of only 14.6% (46/309) for natural conception. The live birth rate of 39.4% in the aforementioned systematic review is broadly consistent with the value of 35.5% for women in our study that had given birth at the time of the analysis. What' more, the clinical pregnancy rate of 41.9% was close to the data of 51.2% in our center during the same time period. Overall, pooled pregnancy rates following conservative treatment for AEH or EC range from 28% to 35% [11-15]. These studies all illustrated that ART is an effective technique for achieving pregnancy after conservative management of these endometrial lesions.

A potential risk of IVF-ET in patients that have been treated for

AEH or EC is disease recurrence, since ovarian stimulation with supra physiologic dosages of gonadotropins can expose the endometrium to high estrogen levels [24]. Ovarian stimulation during IVF can induce estrogen levels as high as 3000-4000 pg/mL (albeit transiently), as compared with a peak level of 300 pg/mL in a natural ovulatory cycle [25]. Whether this high estrogen exposure promotes the recurrence of endometrial lesions remains unknown. The recurrence rate in the present study was only 6.45%, indicating that the use of ART after conservative therapy for AEH or EC carries quite a low risk of disease recurrence. In previous studies, the recurrence rate after conservative treatment of well-differentiated, early-stage EC or AEH has been reported to range from 23% to 47% [11-15]. Although our recurrence rate was notably lower than values determined by previous investigations, this might be related to a shorter follow-up period in our study [26,27].

Only a small number of investigations have directly assessed the influence of infertility treatment on the recurrence of early-stage EC or AEH. Ichinose et al. [23] studied the recurrence rate after infertility treatment in patients with well-differentiated, early-stage EC or AEH that showed complete reversion of the endometrium. With a follow up of 2 years, recurrence was more common in women not given infertility treatment, probably because the pregnancy itself may produce a protective effect on the endometrium, Chao et al. [28] studied clinical outcomes in patients who achieved pregnancy after conservative treatment of EC and found that the disease recurrence rate was not higher in those who received IVF than in those who did not. The aforementioned findings indicate that the use of ART does not increase the risk of AEH/EC recurrence after conservative treatment. Nonetheless, not all studies concur. For example, Althuis et al. [29] showed that CC might increase EC risk in a dose-dependent manner; however, most of the patients undergoing infertility treatment had an ovulatory disorder, which is itself a risk factor for the occurrence of EC.

The fertilization rate, implantation rate and pregnancy rate observed for the 31 patients in our study were broadly similar to values obtained for the general population in our center during the same period of time.

Conclusion

We conclude that endometrial lesions do not impair the IVF process and that outcomes after complete reversion of the endometrium lesion are similar to those seen for the general population.

Assisted reproductive technology is a good option in well-selected patients with early-stage EC or AEH who show complete reversion of the endometrial lesion after conservative therapy. Nonetheless, additional longer-term studies are needed to compare disease recurrence rates and live birth rates between patients given infertility treatment after complete reversion of the endometrium and those not given infertility treatment.

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