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Short Communication

# Obstetric outcomes of pregnancy after conservative treatment of endometrial cancer: Case series and literature review

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**Abstract**

*Objective*: To evaluate the pregnancy courses and obstetric outcomes in patients conceived after conservative treatment of endometrial cancer.
*Materials and Methods*: Case series and systemic review of pregnancy women after fertility-sparing treatment of endometrial cancer. Patients with early stage endometrial cancer were identified through Tumor Registry in Chang Gung Memorial Hospital between 1990 and 2005 and MEDLINE search. Diagnosed cases were managed by fertility-sparing therapies. Pregnancies followed by assisted reproductive technology and spontaneous or ovulation with intrauterine insemination were designated as Group 1 and Group 2, respectively.
*Results*: Five livebirths in three patients with two sets of twin pregnancy were delivered. Adding 47 women in the MEDLINE search literature, there were 65 deliveries with 77 livebirths. Groups 1 and 2 had 15 and 50 deliveries, respectively. Group 1 had 23 livebirths including four sets of twins and two sets of triplets, whereas 54 livebirths consisted of two sets of twins and one set of triplets were noted in Group 2 ($p = 0.003$). Seven preterm deliveries were noted in Group 1 and three in Group 2 ($p = 0.001$). Cesarean rate was 93.3% versus 22.0% ($p < 0.001$) in Groups 1 and 2, respectively. Pregnancy-induced hypertension and gestational diabetes mellitus were significant between the two groups ($p = 0.035$). One mother died of disease after delivery. No neonatal morbidity was reported.
*Conclusions*: For women who had completed conservative treatments in early endometrial cancer, assisted reproductive technology provided a choice of scheduled conception for those with subfertility or chronic anovulation.


*Keywords:* Assisted reproductive technology; Conservative treatment; Endometrial cancer; Pregnancy

## Introduction

The prevalence of endometrial cancer in women younger than 40 years of age is 3–5% and tends to be well-differentiated and early stage disease [1]. The standard treatment for Stage I Grade I carcinoma is total hysterectomy with bilateral salpingo-oophorectomy [2]. Some of these women who wish to preserve fertility may not want to undergo definitive surgical treatment. Kempson and Pokorny [3] reported the first case of term pregnancy by using progestational agents in well-differentiated adenocarcinoma of the endometrium in 1968. Cases of successful pregnancies under conservative management using endometrial curettage and high-dose progestins to treat endometrial cancer were reported thereafter [3]. However, many of these women suffered from infertility or subfertility with underlying disorders such as chronic anovulation, obesity, and/or polycystic ovarian syndrome. With the advance of assisted reproductive technology (ART), pregnancies in these subfertile women have been reported [4–6]. It has been of limited understanding in assistance with ART to conception and a paucity of data in obstetric outcomes in these selected women. In this report, we compared the pregnancy courses and obstetric outcomes in patients conceived after conservative treatment of endometrial cancer in tertiary referral center through a meta-analysis.

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## Materials and methods

The tumor registry at the Chang Gung Memorial Hospital was searched to identify patients younger than 40 years of age who were diagnosed with endometrial cancer between 1990 and 2005. Three patients with conservative management followed by subsequent conception were included in this study [7,8]. Furthermore, a literature search through MEDLINE database was conducted to identify young patients using the term "endometrial cancer", with subheadings of "pregnancy" and "conservative treatment" in English language literature from 1968 to 2005.

The bibliographies of these reports were also searched for additional publications. Use of *in vitro* fertilization (IVF), intracytoplasmic sperm injection, gamete intrafallopian transfer, or zygote intrafallopian transfer was designated as Group 1. Spontaneous pregnancy or ovulation induction with intrauterine insemination was designated as Group 2. Forty-seven women had pregnancies either by Group 1 or Group 2. Two cases had miscarriages with no successful pregnancy were excluded. Univariate analyses included $\chi^2$ tests and Fisher's exact probability tests. A two-tailed value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using statistical software SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

The present study addresses the clinicopathological parameters of pregnancy and obstetric outcomes of patients with endometrial cancer in these two groups.

## Results

Between 1990 and 2005, 20 patients younger than 40 years of age diagnosed with endometrial cancer were retrieved from the Tumor Registry of Chang Gung Memorial Hospital. Three cases with Grade 1 adenocarcinoma had conception with seven pregnancies that resulted in four successful deliveries, six livebirths, one ectopic pregnancy, and two fetal losses. One woman underwent IVF for infertility. Complicated antepartum courses such as gestational diabetes mellitus (GDM), preeclampsia, and preterm delivery were noted in two of the three women. One patient conceived twice and underwent hysterectomy during her second cesarean surgery. Two patients received subsequent hysterectomies after achieving successful livebirths. The details of these patients are shown in Table 1.

Literature search identified 47 additional patients who had documented endometrial cancer and conceived after conservative treatment. All except one with an adenosquamous had adenocarcinomas. Forty-four women had Grade 1 and three had Grade 2 differentiation. Various progestin-based hormonal regimens were used in most of these patients with a few added tamoxifen.

Overall, Group 1 ($n = 14$ women) had pregnancy after IVF, intracytoplasmic sperm injection, gamete intrafallopian transfer, or zygote intrafallopian transfer, and Group 2 ($n = 36$ women) consisted of cases who had spontaneous conception or had ovulation induction with intrauterine insemination (Table 2). Age at diagnosis ($32.1 \pm 4.1$ years *vs.* $29.5 \pm 5.3$ years) and age

Table 1
Clinical features of three patients with early stage endometrial cancer

| Authors | Treatment | Parity | Age at diagnosis | Histology type | Pregnancy course | Gestational week at delivery | Mode of delivery | Postpartum outcome |
|---|---|---|---|---|---|---|---|---|
| Wang et al [7] | T + M | G2P2 | 31 | adenoCA | Singleton pregnancy at 18 mo after diagnosis and twin pregnancy 46 mo after diagnosis | Term | C/S, twice | TAH at second C/S; NED for 16 yr |
| Wang et al [7] | T + M | G5P1AS3 | 30 | adenoCA | Right tubal pregnancy at 12 mo after diagnosis followed by two abortions, one 25-wk IUFD at 36 mo, and a successful spontaneous pregnancy at 67 mo after diagnosis | 28[a] | C/S | TAH; NED for 8 yr |
| Wu et al [8] | M | G1P1 | 32 | adenoCA | Twin pregnancy at 39 mo after diagnosis undergoing IVF-ET | 35 | C/S | TAH; NED for 10 yr |

[a] Alive baby with pregnancy termination because of severe preeclampsia and intrauterine growth retardation.
adenoCA = adenocarcinoma; C/S = cesarean section; IUFD = intrauterine fetal demise; IVF-ET = *in vitro* fertilization-embryo transfer; NED = no evidence of disease; T + M = tamoxifen and megace; TAH = total abdominal hysterectomy.

Table 2
Distribution of clinicopathological characteristics in the endometrial cancer patients with conception in the meta-analysis

| Characteristics | Patients no. | Group 1 | Group 2 | *p* |
|---|---|---|---|---|
| Age at diagnosis, yr (mean ± SD) | 50 | 32.8 ± 4.1 ($n = 14$) | 29.5 ± 5.3 ($n = 36$) | 0.05 |
| Age at pregnancy, yr (mean ± SD) | 43 | 34.3 ± 4.0 ($n = 13$) | 30.9 ± 5.3 ($n = 30$) | 0.05 |
| Histology type | 45 | 14 | 31 | 1.0 |
| Adenocarcinoma | 44 | 14 | 30 | |
| Adenosquamous | 1 | 0 | 1 | |
| Grade of differentiation | 41 | 14 | 27 | 1.0 |
| Well | 38 | 13 | 25 | |
| Moderate and poor | 3 | 1 | 2 | |
| Hysterectomy after childbearing | 50 | 14 | 36 | 0.70 |
| Yes | 9 | 3 | 6 | |
| No | 41 | 11 | 30 | |
| Metastasis/recurrence | 50 | 14 | 36 | 0.57 |
| Yes | 4 | 0 | 4 | |
| No | 46 | 14 | 32 | |
| History of infertility | 35 | 14 | 21 | 0.64 |
| Yes | 31 | 13 | 18 | |
| No | 4 | 1 | 3 | |
| Ovulation induction rate | 50 | 14 | 36 | <0.001 |
| Yes | 24 | 14 | 10 | |
| No | 26 | 0 | 26 | |
| Miscarriage rate | 50 | 14 | 36 | 1.0 |
| Yes | 5 | 1 | 4 | |
| No | 45 | 13 | 32 | |

SD = standard deviation.

of pregnancy (34.3 ± 4.0 years *vs.* 30.9 ± 5.3 years) were not significantly different between the two groups ($p = 0.05$). Group 1 had 23 livebirths including four sets of twins and two sets of triplets, whereas 54 livebirths consisted of two sets of twins and one set of triplets in Group 2. Table 3 shows 65 deliveries and their obstetric outcomes; Groups 1 and 2 had 15 and 50 deliveries, respectively. Group 1 had more multiple gestations ($p = 0.003$), more preterm deliveries ($p = 0.001$), higher cesarean rate ($p < 0.001$), and more obstetrical complication ($p = 0.035$) than Group 2. One woman in Group 2 suffered from GDM with pregnancy induced hypertension, whereas three women (1 case each had hemolysis, elevated liver enzymes, and low platelet syndrome, preeclampsia, and GDM with pregnancy induced hypertension) were found in Group 1.

## Discussion

Preserving reproductive potential has become an important issue in endometrial cancer diagnosed in young women before the age of 40 years because of delayed childbearing, and the survival rates in these reproductive-age women with endometrial cancer are favorable. These women are frequently nulligravid with history of infertility, but have strong desire to preserve fertility. Pregnancies have been reported, mostly after endometrial curettage and successful hormonal therapies for early stage, low-grade endometrioid adenocarcinoma in young women since 1968 [3–6,8–24]. The advent of efficient ART helped in achieving successful pregnancies with increasing reported cases after 1990 [25–34]. The rationale for immediate

Table 3
Analyses of obstetric outcomes according to undergoing IVF, ICSI, gamete intrafallopian transfer, or zygote intrafallopian transfer (Group 1) and spontaneous conception/intrauterine insemination (Group 2)

| | Group 1 ($n$=15) | | Group 2 ($n$=50) | | *p* |
|---|---|---|---|---|---|
| Preterm labor | 7 (46.7) | | 3 (6.0) | | 0.001 |
| Cesarean rate | 14 (93.3) | | 11 (22.0) | | <0.001 |
| Primigravida | 14 (93.3) | | 36 (72.0) | | 0.160 |
| Multiple pregnancy | 6[a] (40.0) | | 3[b] (6.0) | | 0.003 |
| Obstetric complications | 3 (20.0) | HELLP syndrome, preeclampsia, GDM with PIH | 1 (2.0) | GDM with PIH | 0.035 |

[a] Four twins and two triplets; [b] Two twins and one triplet.
Data are presented as *n*(%).
GDM = gestational diabetes mellitus; HELLP syndrome = hemolysis, elevated liver enzymes and low platelet syndrome; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; PIH = pregnancy induced hypertension.

ART of the sub/infertility patients was to avoid prolonged unopposed estrogen stimulation with the risk of reinduction of neoplastic endometrial lesion by estrogen [26]. Although these cases were not numerous, clinical experience has shown the effectiveness of such therapies in patients with early endometrial cancers.

It is evident that either megestrol acetate (megace) or medroxyprogesterone acetate is effective for hormonal treatment of early stage endometrial cancer after endometrial curettage [12,17,35]. Common regimen includes megace (40–160 mg/day) or medroxyprogesterone acetate (100–800 mg/day) for 6 months. The median length of treatment for complete response was 3 months (range, 1–12 months) [35]. These patients were followed up every 3–4 months by serial sonography, hysteroscopy, transcervical resection of endometrial tissue for pathological proof if necessary, and magnetic resonance imaging. However, there was no consensus on the timing of ART, but to initiate as soon as the patient achieved remission or after having two consecutive normal endometrial samplings in periodic samplings every 3–6 months [19].

This meta-analysis demonstrated a significant increase in hypertensive disorders, preterm labor, multiple pregnancies, and the incidence of cesarean delivery in infertile women undergone ART. The increased cesarean rate in these women appears to be associated with multiple pregnancies, preterm labor, and obstetric complications. Increased number of multiple pregnancies in this study could be the result of ovulation induction with gonadotropins and clomiphene citrate. The reason of infertile women undergone ART might be because of chronic anovulation. This also leads to increased number of GDM, which may be reflected by glucose intolerance and other metabolic disorders [36]. Nevertheless, placental abruption, placental abnormalities, fetal chromosome, or structural abnormalities were insignificant between women who underwent ART and women who conceived spontaneously in this meta-analysis.

Long-term surveillance is required even after delivery for the risk of cancer recurrence. Recurrences are common, with a median of 40 months in the patients preserving fertility [19,35]. Three cases had local recurrence including an early ovarian metastasis after a successful term pregnancy in this study [7,16,18]. Furthermore, a woman died of cancer progression 8 months after a term delivery [21]. Hysterectomy for the purpose of avoiding cancer recurrence after complete childbearing is proposed [12].

Limitation of this study is inadequate data of collected cases used for analysis because of some missing data. However, the knowledge of ART and pregnancy complications will be useful for physicians and the patients. Clinicians caring for such patients should be vigilant for signs or symptoms of GDM, preeclampsia, and preterm labor during antenatal care.

In conclusion, although young patients with endometrial cancer should be validated on a large sample size, the increasing number of successful conservative treatments with adequate diagnostic facilities may allow tailored ART in selected patients. The age may not play a key role in deciding these young patients undergoing ART; chronic anovulation or polycystic ovarian syndrome may interfere with these clinical settings. Nevertheless, ART patients were associated with increased risk of preterm labor, preeclampsia, tended to have multiple gestations and higher cesarean rate.

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