

Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma

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Objective: To reduce estrogen exposure in women with endometrial cancer undergoing in vitro fertilization using an aromatase inhibitor.

Design: Prospective case series.

Setting: Academic center for reproductive medicine.

Patient(s): Endometrial carcinoma patients presenting for fertility preservation or fresh embryo transfer to gestational carrier.

Intervention(s): Four patients with endometroid carcinoma underwent five IVF cycles for immediate or delayed embryo transfer to gestational carriers before or after staging and definitive surgery. To prevent surge in E₂ levels, letrozole was started 2 days before gonadotropin administration and then given concomitantly. Embryos were either cryopreserved for fertility preservation or transferred freshly to a surrogate.

Main Outcome Measure(s): Peak E₂ level during stimulation, pregnancy in a gestational carrier.

Result(s): Peak E₂ level during stimulation was 386.67 ± 102.93 pg/mL. A mean of 7 ± 2.85 oocytes were retrieved, resulting in 4.8 ± 1.76 embryos per cycle. In one patient, two embryos were transferred to a surrogate, resulting in a triplet pregnancy. The delivery occurred at 31 weeks and the infants did not show any congenital or developmental abnormalities. Three patients had their embryos cryopreserved for future use.

Conclusion(s): The use of letrozole and gonadotropins is associated with lower E₂ levels compared with standard stimulation cycles in endometrial carcinoma patients. Combination of this approach with surrogacy may enable these young women to preserve their fertility. (Fertil Steril® 2007;88:657–64. ©2007 by American Society for Reproductive Medicine.)

Key Words: Letrozole, controlled ovarian stimulation, endometrial carcinoma

It is estimated that uterine corpus cancer will have affected about 41,000 women in the U.S. in 2005 (1). Endometrial carcinoma is relatively rare before the age of 40, accounting for about 2%–14% of all cases (2). The probability of developing uterine cancer between birth and age 39 is about 0.05%. According to SEER (Surveillance Epidemiology End and Result) data, the prevalence of uterine cancer in the 27 years ending January of 2002 in women between ages of 20 and 44 years is approximately 12,000 cases (3).

Young patients with endometrial carcinoma may present with infertility, irregular bleeding, thick endometrium, or uterine polyps (4). Unopposed estrogen exposure (due to chronic anovulation, polycystic ovary syndrome, and estrogen-secreting ovarian tumors) is a common underlying risk

factor. The accepted treatment of endometrial cancer in young women poses a challenge to the clinician because it requires total abdominal hysterectomy (TAH) and bilateral salpingoophorectomy (BSO). However, many of these women have not yet initiated or completed childbearing. These women have been limited in their options for fertility preservation. Ovarian stimulation for oocyte or embryo freezing is typically avoided in these patients, because of the exposure of their estrogen-dependent tumor to higher doses of estrogen may not be safe.

Progestin treatment has been the main approach to preserving fertility in women with stage 1, grade 1–2 endometrial carcinoma (2). Analysis of 101 cases reported in the literature revealed an initial response of about 70% after one course of treatment which lasted for an average 3.6 months (4). Those who do not qualify for conservative management or who do not respond to progestin treatment require a staging laparotomy, TAH, and BSO with pelvic and possibly periaortic lymphadenectomy. Because embryo cryopreservation is the most established method of fertility preservation (5), these women could, in theory, undergo ovarian stimulation for in vitro

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fertilization (IVF) before surgery. However, because of the estrogen-sensitive nature of endometrial cancer, that approach has generally been avoided.

Third-generation aromatase inhibitors (letrozole, anastrozole and exemestane) became available as first- and second-line treatment agents for patients diagnosed with breast cancer (6, 7). Recently, aromatase inhibitors were used for the treatment of early and advanced stages of endometrial carcinoma.

We have previously described the use of letrozole in combination with FSH for ovulation induction to cryopreserve embryos in breast cancer patients before chemotherapy (8). In that study, we found that the combined letrozole-FSH protocol resulted in peak E₂ levels close to those seen in unstimulated cycles, and breast cancer recurrence rates were not increased compared with control subjects.

We now report a novel use of letrozole to preserve fertility by embryo cryopreservation or fresh embryo transfer to gestational carriers in women diagnosed with early-stage endometrial carcinoma to allow ovarian stimulation without a significant rise in estrogen levels.

MATERIALS AND METHODS

Patients

Four patients presented to the Center for Reproductive Medicine and Infertility with a diagnosis of endometroid carcinoma and desired fertility preservation before definitive surgical management. All patients initially presented to their gynecologists with irregular menstrual cycles or menometrorrhagia (Table 1).

Patient A The patient was a 32-year-old nulliparous woman. Uterine polyps were detected by sonohysterogram. Dilation and curettage (D&C) revealed International Federation of Gynecology and Obstetrics (FIGO) grade 2 endometroid carcinoma and adenomatous hyperplasia with atypia. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed that carcinoma was invading more than half of the myometrial thickness and the absence of extrauterine disease. Chest x-ray was negative. She was placed on megesterol acetate (Megace) 160 mg per day for a total of 2 years. Letrozole 2.5 mg per day was added (9) in the last 6 months. The D&C and MRI were repeated every 3–5 months. Subsequent MRI studies did not reveal any uterine abnormalities. The D&C initially reverted to complex hyperplasia with atypia in 3 months and complex hyperplasia without atypia after 7 months. A subsequent D&C revealed complex hyperplasia with atypia. Letrozole was added for 6 months, but atypical hyperplasia persisted. Definitive surgical treatment was then decided upon with the possibility of ovarian preservation if no extrauterine disease was found.

Patient B A 29-year-old patient with polycystic ovary phenotype presented to her gynecologist for evaluation of menometrorrhagia. A D&C and hysteroscopy revealed a FIGO grade 1 endometroid carcinoma. An MRI did not detect

Demographic and clinical characteristics.								
Patient	Age ^a	G/P	BMI	Presentation	Stage	Grade	Treatment	Hysterectomy ^b
A	32	0/0	31.2	Menometrorrhagia, uterine polyps	Ic	1	Megasterol 1.5 yrs +letrozole 6 m	After 1st IVF (24 m)
B	29	0/0	24.6	Menometrorrhagia, PCO	Ia	1	Megace 2.5 yrs	Before IVF (30 m)
C	31	0/0	40	Irregular periods, PCO	Ia	2	None	After IVF (3 m)
D	39	2/1	25	Menometrorrhagia, uterine polyp	Ia	2	None	After IVF (2 m)
^a Age at presentation for fertility preservation.								
^b Numbers in parenthesis indicate months (m) between diagnosis and definitive surgical treatment.								
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myometrial invasion. She was started on megestrol acetate 160 mg per day and continued for 2.5 years. She was followed up with D&C hysteroscopy every 4–6 months. Endometrial histology indicated complex hyperplasia with atypia. This pathology persisted in subsequent biopsies. Patient was referred for IVF treatment to preserve her fertility before hysterectomy.

Patient C A 31-year-old nulliparous woman with polycystic ovary syndrome underwent D&C for evaluation of irregular uterine bleeding. Pathologic analysis revealed FIGO grade 1 endometroid adenocarcinoma. An MRI revealed no myometrial invasion or extrauterine disease. She was referred for fertility preservation by IVF before hysterectomy.

Patient D The patient was a 39-year-old, G2P1011 on presentation. A D&C and hysteroscopy revealed FIGO grade 2 endometroid carcinoma. The tumor was estrogen and progesterone (P) receptors positive. Pelvic MRI did not reveal extrauterine disease. She was referred for fertility preservation by embryo cryopreservation before definitive surgical management.

IVF Protocol

The ovarian stimulation protocol was approved by the Institutional Review Board of Weill Medical College of Cornell University. A written informed consent was obtained from each patient. In addition, the oncologist’s approval was obtained before treatment. Letrozole 5 mg per day (Femara, Novartis, East Hanover, NJ) was administered starting on the second day of the menstrual cycle if the patient had an intact uterus. If the stimulation was performed after hysterectomy, beginning of the menstrual cycle was determined by serial E₂ and P measurements and transvaginal ultrasound examinations. This was followed 2 days later (cycle day 4) by the daily administration of recombinant FSH 112–225 U (Gonal-F; Serono, Rockville; or Follistim; Organon, West Orange, NJ). A GnRH antagonist (Ganirelix 250 µg per day; Organon) was administered when E₂ was ≥ 300 pg/mL

or the lead follicle size reached 13 mm. Human chorionic gonadotropin was administered when the leading follicle reached 19–20 mm in diameter (8). A transvaginal oocyte retrieval was performed 36 hours later, and the resulting oocytes were fertilized by intracytoplasmic sperm injection. To prevent a rebound increase in E₂, letrozole treatment was restarted after oocyte retrieval until levels fell below 50 pg/mL (Fig. 1).

RESULTS

Outcomes of Ovarian Stimulation With Letrozole

Two patients (C and D) underwent ovarian stimulation before the surgery and one patient (B) was stimulated after surgery. Patient A was stimulated before and after surgical staging. The average peak E₂ level during stimulation was 386.67 ± 102.93 pg/mL. A mean of 7 ± 2.85 oocytes were retrieved per initiated cycle, resulting in a mean of 4.8 ± 1.76 embryos. Table 2 presents the clinical management and IVF results in these patients. In the first cycle of patient A, letrozole was used alone before hysterectomy, while the patient had just discontinued progestin treatment and was still amenorrheic. This cycle yielded two embryos. Subsequently a total abdominal hysterectomy with ovarian conservation was performed. After the surgery, these embryos were thawed to be transferred to her sister but did not survive on thawing. Afterwards, the patient was stimulated using letrozole and FSH, but the cycle was canceled owing to premature ovulation. In the subsequent cycle, in addition to ovarian stimulation with letrozole and FSH, a GnRH antagonist was used to prevent premature ovulation. The resulting fresh embryos were transferred to a synchronized gestational carrier (sister). Two 8-cell embryos resulted in a triplet pregnancy. Pregnancy was complicated by preeclampsia and preterm labor. Cesarean delivery was performed at 31 weeks of gestation, resulting in the delivery of three baby girls (1300–1450 g) with no birth defects. Two were monozygotic twins and required ICU admission for about 4 weeks. They are presently 2 years old

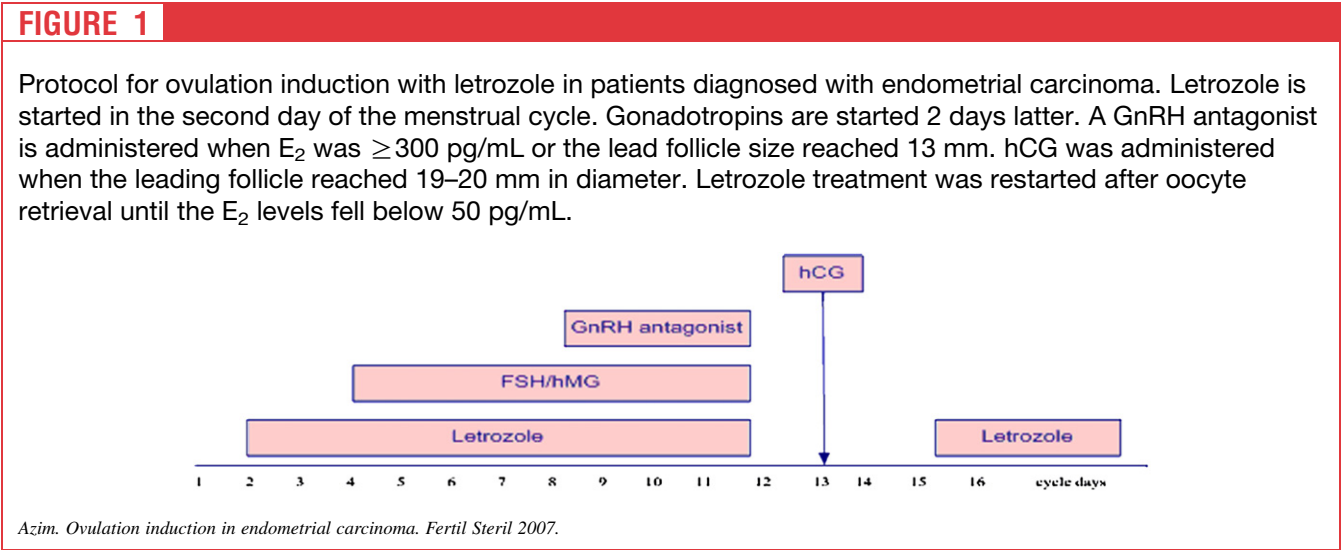


TABLE 2

Results of IVF after ovarian stimulation with letrozole in endometrial carcinoma patients.

Patient	Protocol	E ₂ on hCG day (pg/ml)	Length of COH (d)	Oocytes retrieved	Mature oocytes	Oocytes fertilized	Embryos frozen
AI	Letrozole 5 mg × 5 d	118	7	2	2	2	2
AI	Letrozole, FSH 150 U, ganirelix	353	14	Canceled owing to premature ovulation	—	—	—
AIII	Letrozole, FSH 225 U, hMG 225 U, ganirelix	774	18	19	13	10	0
B	Letrozole, FSH 112 U	241	10	10	9	8	8
C	Letrozole, FSH 150 U	228	12	4	3 ^a	1	1
D	Letrozole, FSH 300 U, ganirelix	606	10	10	8	8	8

Note: COH = controlled ovarian hyperstimulation.

^a After in vitro maturation.

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and do not show any developmental delay. The other two patients had their embryos frozen for future use (Table 2).

Cancer Treatment Outcomes and Patient Follow-Up

All patients except patient A were completely staged. None required any adjuvant therapy. In Patient A, definitive surgery was performed 24 months after the initial diagnosis. Hysterectomy revealed complex hyperplasia with atypia. She did not undergo BSO until then and did not have any evidence of disease 3 years after the hysterectomy.

After her IVF cycle, patient B underwent TAH, BSO, and staging approximately 30 months after her initial diagnosis. Stage Ia endometroid carcinoma was detected. Two and a half years after the hysterectomy, the patient has no evidence of disease.

Patient C underwent staging, TAH, BSO, and lymph node sampling 3 months after the initial diagnosis. This indicated a stage Ia, FIGO grade 1 endometroid carcinoma. The patient remained free of disease 2 years after her hysterectomy.

Patient D underwent staging laparotomy, TAH, and BSO with pelvic lymph node sampling 2 months after the diagnosis. Staging revealed a stage Ia, FIGO grade 2 disease. The length of the follow-up period was less than 3 months with no recurrence reported.

DISCUSSION

In earlier studies where assisted reproductive technologies were used in cases with existing endometrial cancer, typically the endometrium was “normalized” with high-dose progestin treatment before attempting IVF with conventional stimulation protocols (10–19) (Table 3). Those stimulation regimens generally expose patients to high estrogen levels, and, with the exception of a case by Juretzka et al. (19) where a progestin-impregnated intrauterine device was inserted during stimulation, no attempt was made to protect the endometrium against the effects of estrogen.

Although the consolation for using standard IVF protocols and the delay in surgical treatment in these patients was the fact that they had early-stage endometrial cancer, most of those case reports relied on clinical staging combined with imaging (computerized tomography or MRI). Because clinical staging can underestimate the extent of the disease in about 20% of stage I endometrial carcinoma (20) the delay or omission in surgical staging can be detrimental (19). For example, in a series of eight patients where progestagen treatment failed, one had recurrence in the preserved ovary and ultimately succumbed to her disease (2). Moreover the possibility of a synchronous ovarian primary should not be disregarded (15).

Moreover, the safety of exposure to high levels of estrogen was not established, even in early-stage endometrial cancer. Therefore, our purpose was to develop an ovarian stimulation protocol that would offer a wider safety margin, at least in theory, for endometrial cancer patients.

TABLE 3**Earlier studies of IVF in patients diagnosed with endometrial carcinoma.**

Reference	Age	Treatment before IVF	Ovarian stimulation protocol	Peak E ₂ pg/mL	Result	Treatment after IVF
Paulson 1990 (10)	35	Polypectomy, D&C, P	Long GnRHa	NR	Singleton	Progestin, D&C
Sardi 1998 (11)	35	D&C, P	NR	NR	Singleton	NR
Zuckerman 1998 (12)	26	Polypectomy, D&C, P	NR	NR	Twin	Hysterectomy-NED
Shibahara 1999 (13)	32	Laparoscopy, D&C	Long GnRHa	NR	Singleton	D&C
Ogawa 2001 (14)	31	D&C, P	NR	NR	Singleton	D&C
Pinto 2001 (15)	29	Laparoscopy, ovarian diathermy D&C, P	Long GnRHa	2621	Triplet	LAVH/BSO-ovarian adenocarcinoma
Lowe 2003 (2 cycles) (16)	38	D&C, P	NR	NR	No pregnancy	D&C
			Donor oocyte	NR	2 sets of twins	VH, BSO-NED
Yarali 2004 (18)	32	SL, D&C, P	Long GnRHa	NR	Singleton	D&C
Nakao 2004 (2 patients) (17)	37 35	D&C, P D&C, P	NR NR	NR NR	Twin Singleton	D&C
Juretzka 2005 (19)	37	—	P-IUD Embryo cryo. Gestational carrier	NR	Singleton	Cervical involvement (IIB) LAVH/BSO/RT-NED

Note: BSO = bilateral salpingoophorectomy; cryo = cryopreservation; GnRHa = gonadotropin-releasing hormone agonist; LAVH = laparoscopic assisted vaginal hysterectomy; NED = no evidence of disease; NR = not reported; P = progestins; SL = staging laparotomy; P-IUD = progestin-impregnated intrauterine device.

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The use of aromatase inhibitors for ovulation induction was first reported in 2001. The stimulation with letrozole was shown to be superior to clomiphene citrate and was associated with 50% lower E₂ levels (21). We have recently introduced letrozole as an ovarian stimulant in cancer patients. In the first study, we prospectively compared letrozole stimulation with or without gonadotropins to our previously reported approach with tamoxifen and FSH (22) in breast cancer patients, (8). The letrozole-FSH treatment resulted in the cryopreservation of a higher number of embryos while maintaining peak E₂ levels close to those of unstimulated cycles. Recurrence rate was similar to unstimulated control subjects with history of breast cancer. Moreover, we showed that stimulation with letrozole resulted in similar IVF outcomes in breast cancer patients compared with infertility patients undergoing IVF with standard protocols (23).

In the present report, we used letrozole in conjunction with gonadotropins for controlled ovarian stimulation to avoid

high estrogen levels associated with conventional regimens. Moreover, we used synchronized gestational carriers in some patients to achieve pregnancy with fresh embryo transfer. The advantage of using gestational carriers is that the definitive treatment is not delayed and the potential risks of conceiving with inadequate staging are avoided. However, although surrogacy does not pose significant additional costs if performed with a volunteer, e.g., relative, the cost can be substantially higher than standard IVF if paid carriers are used.

We not only chose letrozole for its ovulation induction effect but for its potential safety margin in endometrial cancer patients. Letrozole is a nonsteroidal competitive inhibitor of aromatase enzyme in all tissues, leading to suppression of E₂, estrone, and estrone sulfate by 75%–95% (24). Aromatase gene expression was detected in endometrial carcinoma stroma cells (25). Moreover, aromatase inhibitors have been shown to induce apoptosis in endometrial cancer cells in vitro (26, 27).

The activity and toxicity of aromatase inhibitors in patients with advanced or recurrent endometrial carcinoma were investigated in two prospective phase II studies. Ma et al. (2004) (28), administered letrozole at a dose of 2.5 mg for 4–28 weeks to 32 patients with advanced endometrial adenocarcinoma or adenosquamous carcinoma not curable by surgery or radiotherapy. Patients had minimal toxicity from therapy, and one patient had deep vein thrombosis. Overall response was 9.4%. The Gynecologic Oncology Group (29) conducted a phase II study using anastrozole in 23 patients with advanced endometrial carcinoma. They reported an overall response of approximately 15%. One pulmonary embolism and one DVT were reported. No toxicity occurred due to the treatment. The use of letrozole was not associated with increase in the incidence of adverse reactions over 160 mg/day megesterol acetate.

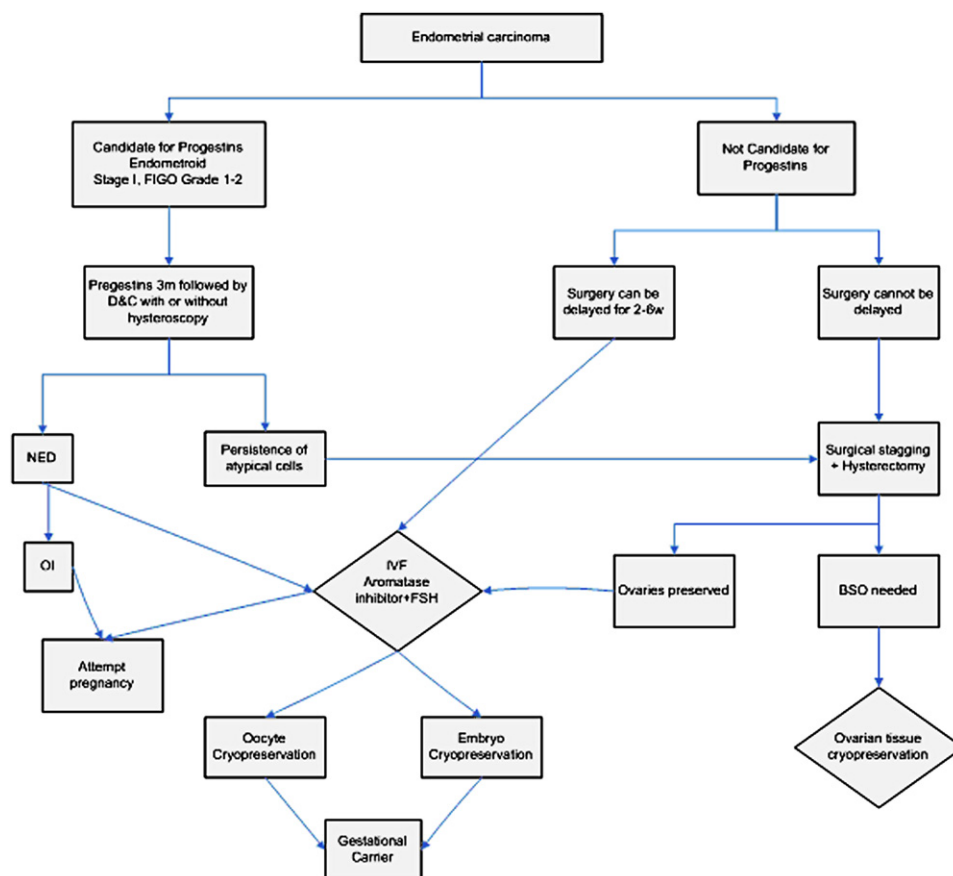
Aromatase inhibitors were also used in early-stage endometrial carcinoma patients. Bernstein et al. (9) reported on the use of 2.5 mg letrozole for 14 days before hysterectomy in postmenopausal women. It was associated with reduction

in lower abdominal pain, vaginal discharge, and endometrial thickness. Obviously, further studies are required to determine the benefit of letrozole, if any, in the treatment of early-stage endometrial carcinoma.

There have been recent concerns regarding the safety of letrozole when used in the setting of ovulation induction (Biljan et al., abstract, American Society for Reproductive Medicine, Montreal, Canada, Oct 15–19, 2005). In the setting of fertility preservation, embryos are not exposed to letrozole, because fertilization takes place in vitro and the embryos are either cryopreserved or transferred to a gestational carrier. Even if the embryos are transferred in the same cycle to the patient herself, exposure to significant levels of letrozole is unlikely, because letrozole has a 48-h half-life. With this half-life, its levels are expected to fall below the therapeutic levels by the time the embryos are implanted (23, 30). Moreover, a recent study (31), detected a 2.4% incidence of chromosomal abnormalities and congenital anomalies in 514 newborns conceived after induction of ovulation using letrozole versus 4.8% of 397 newborns conceived after clomiphene

FIGURE 2

An algorithm for fertility preservation in endometrial carcinoma. See text for explanation. NED = no evidence of disease; BSO = bilateral salpingoophorectomy; OI = ovulation induction.



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citrate use. Not only the incidence of congenital abnormalities were not increased, but also congenital cardiac anomalies were significantly less common in the letrozole group.

Based on our previous experience with breast cancer patients and the recent use of aromatase inhibitors in the treatment of endometrial cancer, we believe that use of letrozole with gonadotropins can be an added layer of protection. While larger studies are needed to prove the safety of this approach, we propose in the meantime the following approach to preserve fertility in young women with early stage endometrial cancer (Fig. 2). High-dose progestins can be used in young women with early stage endometrial cancer with the hope of reversing neoplastic changes and preserving the uterus. Once neoplastic changes are reversed, patients can attempt pregnancy with ovulation induction using letrozole and FSH. If treatment has failed and a definitive surgical procedure is planned, the letrozole + FSH ovarian stimulation protocol can be used to cryopreserve embryos or oocytes (32) for future use. If ovarian removal is needed during surgery, ovarian cryopreservation can be considered, but ovarian involvement may preclude transplantation (33). If oocyte or embryo cryopreservation could not be performed before surgery and the ovaries were preserved, patients can resort to IVF with the letrozole-FSH protocol described here, and the embryos are transferred to a surrogate. Feasibility and safety of this proposed approach is being tested in ongoing prospective studies.

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