Oncological and Reproductive Outcomes for Gonadotropin-Releasing Hormone Agonist Combined with Aromatase Inhibitors or Levonorgestrel-releasing Intrauterine System Fertility-Sparing Treatment in Women with Endometrial Cancer or Atypical Endometrial Hyperplasia: A single-center retrospective analysis of 179 cases

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Research Article

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Abstract

Purpose: To evaluate the efficacy and safety of gonadotropin-releasing hormone agonist (GnRHa) combined with levonorgestrel-releasing intrauterine system (LNG-IUS) or aromatase inhibitor (AI) in women with endometrial carcinoma (EC) and atypical endometrial hyperplasia (AEH) who wish to preserve their fertility.

Methods: 179 EC/AEH patients who were contra-indicated or unsuitable for high-dose oral progestin were included in our study. Patients were treated with the combination of GnRHa with LNG-IUS (group GLI: GnRHa IH every 4 weeks and LNG-IUS insertion constantly) or combination of GnRHa with AI (group GAI: GnRHa IH every 4 weeks and oral letrozole 2.5mg, daily). Histological evaluation was performed every 3-4 months. After achieving complete remission (CR), maintenance treatments including LNG-IUS, cyclical oral contraceptives or low-dose cyclic progestin were recommended until they began attempting to conceive.

Results: Overall, 169 (94.4%) patients achieved CR, 96.7% in AEH and 93.3% in EC patients. The CR rate in GLI and GAI was 93.5% and 95.8%, respectively. The median time to CR was 6 (3-18) months, 4 (3-10) months in AEH and 8 (3-18) months in EC patients. After a median follow up of 27.5 months, 41 (24.3%) women developed recurrence with the median recurrence time of 17 (6-77) months. Of the patients with CR, 134 cases desired to conceive, 42 (32.3%) women became pregnant, 24 (17.9%) of them successfully delivered and 5 (3.7%) were in pregnancy, while 13 of them miscarried.

Conclusion: GnRHa combined treatment achieved good oncological and reproductive outcomes. Future larger multi-institutional studies should be designed to confirm these preliminary findings.

1. Introduction

Endometrial cancer (EC) is one of the most common as well as an increasingly problematic gynecological cancer, whose incidence has gradually risen in recent years[1–3]. EC and its precursor, atypical endometrial hyperplasia (AEH), affect a larger proportion of premenopausal women, including many women of child-bearing age [4]. The standard treatment for this disease requires a hysterectomy with bilateral salpingo-oophorectomy, with or without pelvic sentinel lymph node dissection, pelvic or para-aortic lymphadenectomy. However, this standard treatment results in a permanent loss of fertility while young patients have a strong desire to bear children. Therefore, conservative treatment should be discussed in young patients with early-stage EC or AEH who wish to preserve their fertility.

High-dose progestins including medroxyprogesterone acetate (MPA) and megestrol acetate (MA) have been the mainstay of conservative treatment of AEH and early-stage EC[5–7]. But adverse effects such as weight gain, liver dysfunction and resistance to oral progestins lead to seeking alternative treatments is mandatory. At present, gonadotropin-releasing hormone agonist (GnRHa) plus levonorgestrel-releasing intrauterine system (LNG-IUS) could be used as an alternative to oral-systemic progestin for the treatment

of women with EC and AEH[8]. Besides, combination of GnRHa and Aromatase inhibitors (AIs) has also been reported as an option for preserve women's fertility with EC and proved to have a good response in previous study[9]. Available evidence on effective application of GnRHa based combination treatment so far is very limited and has about few patients. Therefore, further studies should be performed.

The aim of this study was to investigate the efficacy and safety of the combination of GnRHa plus LNG-IUS or AI (letrozole) in young women with EC or AEH.

2. Methods

2.1 Patients recruited

All patients who received GnRHa based therapy were included between January 2013 and December 2020 at the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital (PUMCH). Patients' information was collected from medical records and a prospectively maintained database, which represented a standard protocol was followed for all patients. The inclusion criteria were as follows: (1) Women of 18–45 years old who desire to preserve their fertility; (2) Histologically confirmed AEH or early-stage endometrioid adenocarcinoma, grade 1–2; (3) No signs of myometrial invasion or extra-uterine metastasis by enhanced magnetic resonance imaging (MRI); (4) Patients were contra-indicated or unsuitable for high-dose oral progestin; (5) Written informed consent obtained; (6) Patients were followed up regularly, full text and complete data available. This study was approved by the Ethics Committee of PMCH (S-244).

2.2 Treatments

Two regimens were used: (1) Regime GLI: combination of subcutaneous injection of 3.75 mg GnRHa every 4 weeks and LNG-IUS (Mirena; Bayer Health Care Pharmaceutical Inc) insertion constantly; (2) Regime GAI: combination of subcutaneous injection of 3.75 mg GnRHa every 4 weeks and oral AI (letrozole) 2.5 mg daily. The distribution of the patients to these two regimes was made based on physicians' recommendation and patients' choices. Regime GLI was recommended for patients who had no birth plan in recent years. Women with lager size of uterus, obesity or/and history of PCOS were recommended to receive Regime GAI.

During the process of treatment, weight loss plans including diet control and exercise recommendation were provided to all patients. Outpatient visits were arranged during the treatment, symptoms such as vaginal spotting, abdominal pain were recorded, physical examination including body weight and lab tests including complete blood counts and biochemistry panels were performed. Trans-vaginal ultrasound scan was performed at every visit to assess the endometrium. Histological response was determined by endometrial biopsy under hysteroscopic evaluation every 3–4 months (one course) during the treatment.

2.3 Response Evaluation

Pathological response to treatment was categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined as the absence of evidence of hyperplasia or carcinoma. PR was defined as the regression of AEH or EC to hyperplasia without atypia. SD was defined as the persistence of disease as initially diagnosed. PD was defined as progression to a lesion of higher grade or progressive disease including myometrial invasion, extra-uterine disease, or lymph node metastasis[10]. Patients with PR or SD continued the treatment for an additional 1–2 courses, whereas those with PD were immediately proposed to receive hysterectomy. Those who had not achieve CR after 12 months of therapy were considered to have failed fertility-preserving treatment and were recommend to receive surgery. Once achieved CR, patients who desire to get pregnant were encouraged to conceive or referred to underwent assisted reproductive technology (ART). Those with CR who had no birth plans were prescribed oral contraceptives cyclic progestin or LNG-IUS insertion to prevent recurrence.

2.4 Follow up

After the documentation of CR, all patients were regularly followed up for a prolonged period with 3-6-month intervals. During each follow-up visit, the following information was collected: menstruation period or abnormal vaginal bleeding, results of trans-vaginal ultrasound scan or MRI if necessary, data relating relapse (interval between CR and recurrence, diagnosis of recurrence, treatment and survival outcomes). The pregnancy was confirmed with the heart beat at gestation age. Fertility outcomes including time of gestation, using of ART, obstetrical complications and delivery were also documented. If the patient received hysterectomy, the reason and histological results of the surgery were also collected. The flowchart of method was showed in Fig. 1

Notes: CBC = complete blood counts, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ART = assisted reproductive technology.

2.5 Statistical analyses

Statistical analysis was performed using IBM SPSS for Windows (version 22.0). Categorical variables are summarized in frequency tables, whereas continuous variables are presented as median (range, min-max). Frequency distributions were compared using chi-squared or Fisher’ s exact tests and median values were compared using Mann-Whitney U tests. Logistic regression models were built to determine associations of CR, recurrence and fertility. For all statistical tests, the differences were considered statistically significant when P-values were < 0.05.

3. Results

3.1 Demographics and Clinical manifestations

The clinicopathologic characteristics of the patients are summarized in Table 1. Sixty (33.5%) patients were diagnosed as AEH and 119 (66.5%) were diagnosed as EC. The median age at diagnosis was 31 years, ranging from 21 to 43 years. 163 (91.1%) women were nulliparous, 48 (26.8%) had comorbidity including polycystic ovary syndrome (PCOS) and/or endometriosis and 72 (40.2%) patients were obese. Overall, 107 patients received regime GLI and 72 patients received regime GAI.

Table 1 Clinicopathologic characteristics of the patients

Characteristics	Values, n(%)
n	179
BMI, kg/m2 （median（range）	29.2 (17.7-46.1)
Obesity	72 (40.2%)
Age, years（median（range）	31 (21-43)
Comorbidity	
PCOS	40 (22.3%)
Endometriosis	9 (5.0%)
Histology	
AEH	60 (33.5%)
EC	119 (66.5%)
Regime	
GLI	107 (59.8%)
GAI	72 (40.2%)

Notes: BMI = body mass index, PCOS = polycystic ovary syndrome, AEH = atypical endometrial hyperplasia, EC = endometrial carcinoma, GLI = combination GnRHa and LNG-IUS, GAI = combination of GnRHa and AI

3.2 Treatment Effects

Totally, 169 (94.4%) achieved CR with the 6 months (3-18 months) median CR time (Table2). 10 (5.59%) patients failed to CR, 4 PR and 6 SD, then underwent the hysterectomy with or without lymphadenectomy. According to the postoperative pathological diagnosis, 2 of them were diagnosed as AEH, 7 were diagnosed as stage IA, and one combined with stage IC ovarian endometrial carcinoma. All patients alive without tumor at the final contact.

Table 2 Oncological outcomes of patients

Characteristics	EC (n=119)	AEH (n=60)	Total (n=179)
CR			
CR rate	111 (93.3%)	58 (96.7%)	169 (94.4%)
CR time, month (range)	8 (3-18)	4 (3-10)	6 (3-18)
Recurrence			
Recurrence rate	26 (23.4%)	15 (25.7%)	41 (24.3%)
Recurrence time,month (range)	16 (6-39)	28 (6-77)	17 (6-77)

Notes: CR = complete response, EC = endometrial carcinoma, AEH = atypical endometrial hyperplasia

The CR rate was 96.7% in AEH patients and 93.3% in EC patients (p=0.351) and the median time to CR was 4 months (3-10 months) in AEH patients and 8 months (3-18 months) in EC patients, respectively. At the end of the first therapy course, the CR rate in AEH was higher than EC (65% vs 31.9%, p□0.0001). Similar results were also found in the second course (91.7% vs 72.3%, p=0.003) (Table 3). The CR rate in obese and non-obese patients were 95.3% and 93.1% (p=0.516), in GLI and GAI group was 93.5% and 95.8% (p=0.336), respectively. Patients with weight loss more than 3% of their initial body weight had a higher response rate (98.8% vs 90.9%, p=0.023). The CR rate of group GLI and GAI was 93.5% and 95.8% (p=0.336), respectively.

Table 3 Duration of complete remission

Times	AEH	EC	Total	p-value
1 course	65% (39)	31.9% (38)	43.0% (77)	**□0.0001**
2 courses	91.7% (55)	72.3% (86)	78.8% (141)	**0.003**
3 courses	96.7% (58)	89.1% (106)	91.6% (164)	0.145
Total	96.7% (58)	93.3% (111)	94.4% (169)	0.351

Notes: AEH = atypical endometrial hyperplasia, EC = endometrial carcinoma.

3.3 Adverse Effects

Postmenopausal symptoms such as hot flashes and vaginal dryness was the most common adverse effect (17.3%), followed by irregular bleeding (11.2%) and abnormal liver function (1.7%). The degree of menopause symptoms was minor and no patients received add-back estrogen. IUD dislocation occurred in 2 patients and was resolved by reinsertion of the IUD. The scheduled treatment was not delayed due to these side effects. No treatment-related deaths were identified.

3.4 Follow up

After pathologically CR achieved, 147 patients accepted maintenance treatment including LNG-IUS, cyclical oral contraceptives or low-dose cyclic progestin until they began attempting gestation. Other 22 patients did not receive any treatment, just follow up regularly. After a median follow-up time of 27.5 months (3-92 months), 41 (24.3%) women had developed recurrence (Table 2). The median time to recurrence was 17 months, ranging from 6-77 months. 10 patients who gave up to preserve their uterus chose to receive hysterectomy with or without lymphadenectomy. Extrauterine lesions were identified in 2 patients and received adjuvant therapy after surgery.

31 patients received fertility sparing re-treatment after recurrence, and 26 (83.9%) achieved CR again. Hysterectomy was performed in 3 (9.7%) patients due to SD or PD. The rest of 3 patients were still in treatment at the final contact. No patient died of the disease during this period.

The related factors for recurrence were shown in Table 4. Multivariate analysis indicated that the recurrence rate was higher in patients who over 30 years (32.3% vs 13.8%, p=0.010), and who lost lower than 3% of their weight (32.2% vs 15.1%, p=0.022). The disease-free survival (DFS) of patients were shown in Figure 2.

Table 4 Risk factors of recurrence

Risk factors to recurrence	Univariate analysis HR (95% CI)	P-value	Multivariate analysis HR (95% CI)	P-value
Age: ≥30 years vs <30 years	2.903 (1.340-6.289)	**0.006**	2.935 (1.298-6.639)	**0.010**
AEH vs EC	0.438 (0.157-0.223)	0.155		
Comorbidity: Yes vs No	1.556 (0.728-3.324)	**0.010**	2.098 (0.908-4.848)	0.082
Obesity: Yes vs No	1.758 (0.848-3.756)	0.127		
Loss-weight: <3% vs ≥ 3%	2.654 (1.234-5.658)	**0.010**	2.719 (1.159-6.380)	**0.022**
Maintenance therapy: No vs Yes	1.481 (0.591-3.741)	0.401		

Notes: AEH = atypical endometrial hyperplasia, EC = endometrial carcinoma.

3.5 Fertility Outcomes

After achieving CR, 134 women attempted to get pregnant and 75 (56.0%) women were transferred to receive ART. Totally, 42 (32.3%) patients became pregnant, 24 (17.9%) of them successfully delivered and 5 (3.7%) were in pregnancy, while 13 of them miscarried, 9 at the first trimester and 4 at the second trimester. The median duration from CR to pregnancy was 12 months (1-72 months) (Table 5).

Table 5 Reproductive outcomes

Characteristics	Values, n(%)
Attempts to conceive	134
Natural conception	59 (44.0%)
ART	75 (56.0%)
Pregnancy	42 (32.3%)
Live baby delivery	24 (17.9%)
Ongoing	5 (3.7%)
Miscarriage	13 (9.7%)
Time from CR to pregnancy, month (range)	12 (1-72)

Notes: ART= assisted reproductive technology, CR = complete remission

In univariate analysis, pregnancy rate was superior in patients who were younger than 35 years old (37.6% vs.12.1%, p=0.06). Higher probability was observed in non-obese patients (39.0% vs 19.23%, p=0.016). ART showed high tendency of pregnancy (38.7% vs 13.7%, p=0.066), and high pregnancy rate was observed in IVF-ET (47.8% vs 27.9%, p=0.039). Age and obesity remained significant when multivariate regression analysis was applied (Table 6).

Table 6 Pregnancy related factors

Predictors to pregnancy	Univariate analysis HR (95% CI)	P-value	Multivariate analysis HR (95% CI)	P-value
Age: < 35 years vs ≥35 years	4.373 (1.427-13.406)	**0.006**	5.246 (1.638-16.802)	**0.005**
Comorbidity: Yes vs No	1.194 (0.513-2.782)	0.681		
Obesity: No vs Yes	2.688 (1.184-6.103)	**0.016**	2.598 (1.103-6.119)	**0.029**
AEH vs EC	0.733（0.325-1.656）	0.455		
Loss-weight: ≥3% vs <3%	1.676 (0.800-3.512)	0.171		
IVF-ET: Yes vs No	2.231 (1.031-4.824)	**0.039**	2.098 (0.919-4.790)	0.069

Notes: AEH = atypical endometrial hyperplasia, EC = endometrial carcinoma, ART= assisted reproductive technology, IVF-ET=in vitro fertilization and embryo transfer.

4. Discussion

With increasing incidence of EC in younger women, increasingly women are likely to seek conservative management options. Progestin therapy is widely accepted as the main fertility-sparing treatment for young women with AEH and well-differentiated EC and acquire satisfactory results[5–7]. However, there are still about 20% of these patients who failed to achieve CR, and lost fertility after hysterectomy[11]. Side-effects or contraindications of progestins, such as weight gain or liver dysfunction call for alternative regimes other than oral high dose progestins.[12] .

GnRHa is a group of synthetic compounds which are derived from natural GnRH through substitution of amino acids at position 6 and/or 10[13]. Some studies revealed that GnRHa can affect endometrial cell proliferation not only through the hormonal axis indirectly, but also by acting on the GnRH receptors directly[14, 15]. Therefore, GnRHa could be used in the treatment of endometrial diseases due to its antiproliferative effect on endometrial cells. But the use of GnRHa is still experimental and did not achieve clinical practice. The application of GnRHa for endometrial diseases was initially reported for the management of patients with recurrent EC, resistant to other treatment modalities, with a regression rate as high as 35%[16, 17]. LNG-IUS represents a newly available delivery system for EC treatment[18]. It could provide local intrauterine concentrations many-fold higher than oral progestins. Some researchers used LNG-IUS solely or in combination with GnRHa and reported encouraging results[9, 19, 20]. Letrozole is the third-generation AIs, which can reduce the levels of estrogen by inhibiting estrogen synthesis leading to a reduction in the receptor-mediated growth stimulated in estrogen receptor positive tumors such as EC.

Combination of GnRHa and AIs has been reported as an option for preserve women's fertility with EC and AEH[21, 22]. In this study, we reported a series of patients with EC and AEH treated with GnRHa plus LNG-IUS/AIs. The preliminary results show an encouraging result a little better than or at least comparable to previous oral-progestin studies [23, 24].

In our study, over 90% patients achieved CR, 96.7% in AEH patients and 93.3% in EC patients, suggesting an encouraging result. Most AEH patients achieved CR within 6 months, but the median CR time of EC is about 3–4 months longer than AEH. 18 patients achieved CR after extension of treatment time as long as 9–15 months. Thus, we recommend that these combination regimes be administered for at least 6 months, especially for EC patients. The long-term adverse effect of GnRHa and influence on fertility by repeated curettage need to be noted. It has been documented that 2–3% of bone mass will be loss with 6 months use of GnRH analogs. And it is unclear what's the maximal duration of therapy, whether the add-back therapy should be performed, whether the bone mineral density should be monitored, and whether calcium and bisphosphonates should be added[25]. Considering that over 90% AEH patients acquired complete remission after 2 course of treatments and LNG-IUS could be used solely to treat EC[18. 19], for AEH patients who already achieved PR after 6 months, the use of LNG-IUD alone might be an option to avoid the side effect of GnRHa. But the efficacy and safety were unclear and further research is needed to accumulate experience.

In our study, patients who were obese and lose weight ≥3% have lower response and pregnancy rates, as well as higher recurrence rates, consistent with previous studies[26]. Patients were unable to conceive due to obesity and PCOS, which leading to anovulation and the absence of stimulation of progestin, may also increase the risk of recurrence[27]. Herein, weight control and health consulting are crucial in the whole-lifespan management of fertility-spearing treatment. GnRHa combined therapy have advantage on weight control compared with progestin therapy since we all know that weight gain was a main side effect of high-dose progestin.

Due to the data limitation, we failed to find the biomarker and the possible reason for treatment failure. MMR testing has been proposed in young women desiring fertility-sparing treatment, but the association between MMR and response is unclear [28]. Some articles have proposed that the overall and recurrence-free survival was significantly lower in p53 abnormal and dMMR patient subgroups. Thus, patients with Lynch syndrome and P53 mutations may not be treated conservatively[29]. The status of progesterone receptor (PR) and estrogens receptor (ER) was thought to be associated with disease regression in some research[30–32]. But all patients in our study were ER and PR positive, so, we failed to analyse the relationship between IHC and of CR. As modern The Cancer Genome Atlas (TCGA)-based molecular classification system that has been validated, it might helpful to predict the response and contribute to the selection of population who suit for fertility-preserving.

Previous studies revealed a high rate of relapse, ranging from 10–88%[18, 24]. In our research, about 25% women had developed recurrence with 20 months median recurrence time, consist with former articles.

But some of the recurrences were diagnosed as early as 6–7 months after a CR. Another study report that recurrence occurred 3–4 months after CR which mandates the follow-up to be started early[33]. The latest recurrence in our cohort took place at 7 years in our research, others also report at 13 years[34, 35]. Therefore, long-term and regular follow-up is essential due to the high rate of late recurrence. Additionally, hormonal maintenance therapy is important for complete responders who do not wish to conceive immediately after completion of treatment[36]. And low recurrence rate was also found in patients with pregnancy. Therefore, maintenance therapy and conception immediately were encouraged to reduce the risk of recurrence.

The pregnancy and live birth rates in our research are still somewhat suboptimal, lower than other large studies about progestin[23, 37]. This might be due to endometrium atrophic decreased by repeated hysteroscopic evaluation and curettage. But the miscarriage rate at the first or second trimester are in accordance with ordinary population[38]. The follow up time in our study was relatively short, if longer follow-up time were performed, high rate of relapse and live birth may be observed[39]. Despite our expectations ART did not significantly improve the live birth rate, women who choosing IVF-ET had a relatively better results and some studies did report improved birth rate with ART[40, 41]. Hence, once CR has been achieved, pregnancy should be carried out as soon as possible, and IVF-ET is recommended without causing significant delays.

Strengths and limitations

To the best of our knowledge, the current study included the largest number of subjects of both oncologic and reproductive results about GnRHa based treatments. The findings confirm that the combination of GnRHa with LNG-IUS/letrozole is an effective method with high rate of regression and minor side effects. But there are still some limitations. Firstly, it is a single-center retrospective study, multi-center prospective clinical trials are supposed to conducted to verify the suitability of the combination of GnRHa with LNG-IUS/letrozole use for fertility preservation. Secondly, the follow-up time of this center is limited, and long-term follow-up of these patients will also be performed to verify high pregnancy rate. Thirdly, as the modern TCGA-based molecular classification system is being introduced, it would be necessary to assess responses and recurrences in all future conservatively treated EC patients from this molecular perspective. Fourthly, long-term side-effect of GnRHa such as osteoporosis and the cardiovascular complications should be considered in future observation.

Conclusion

In conclusion, the findings of our study confirm that the combination of GnRHa with LNG-IUS/letrozole is an effective method with high rate of regression. Besides, the recurrence and pregnancy rate are comparable to traditional oral-progestin therapy. So, the combination of GnRHa with LNG-IUS/letrozole is an encouraging alternative regime for fertility-preserving of EC and AEH patients who were contra-indicated or unsuitable for high-dose oral progestin.

Declarations

Author contributions

JC, JY, DC, and KS: conceived and designed the study. JC, MY, HZ, JW, YZ, NC, and PP: data acquisition. JC, and DC: analyzed the data. JC: wrote the original draft. JY, DC, and KS: wrote, reviewed, and edit. All authors contributed to the article and approved the submitted version.

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Figures

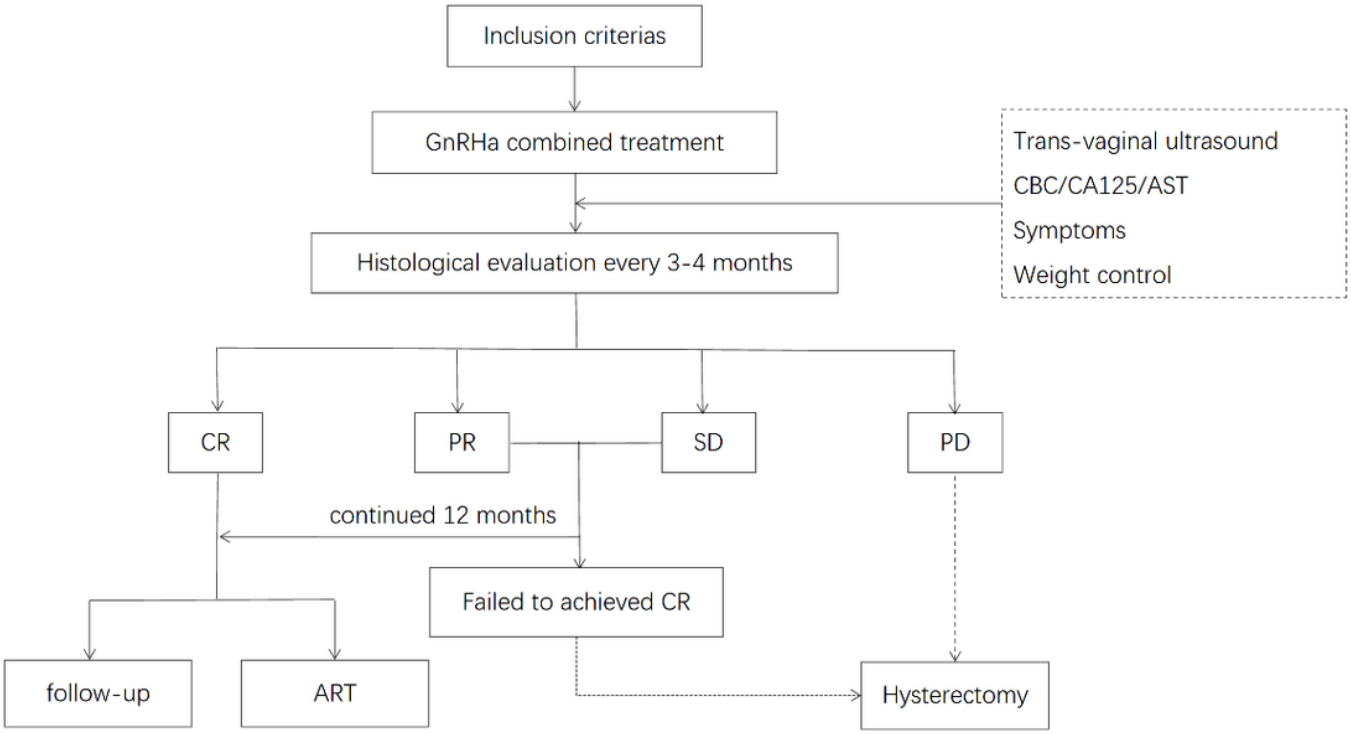

Figure 1

The flowchart patients received GnRHa based treatment

Notes: CBC = complete blood counts, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ART = assisted reproductive technology.

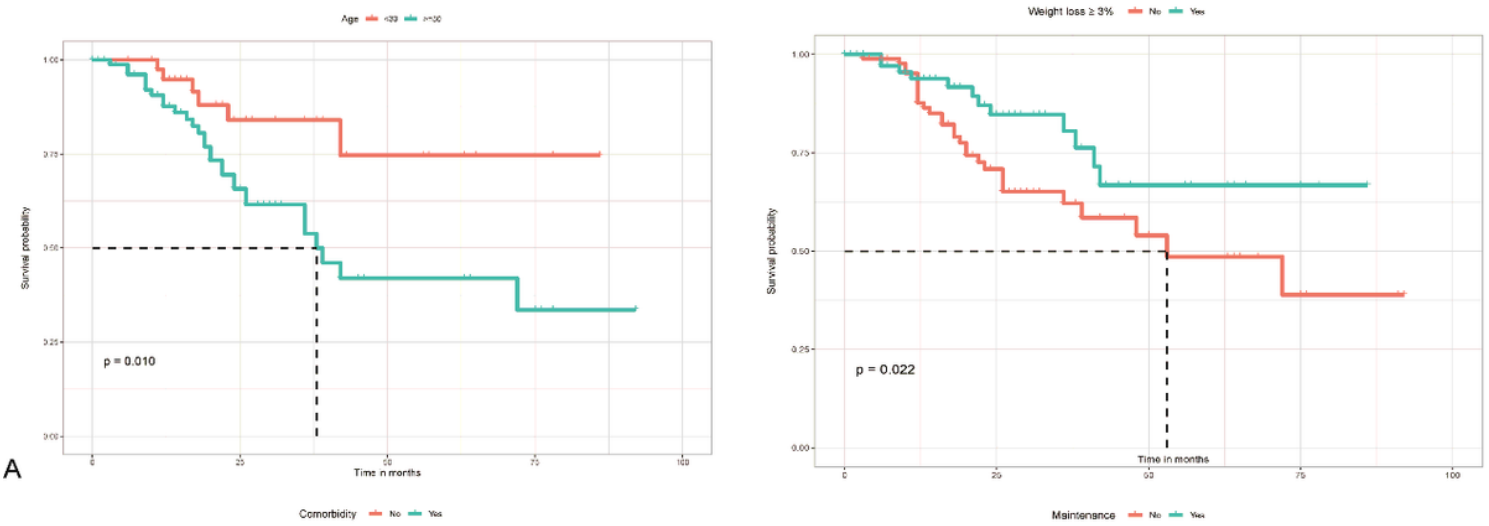

Figure 2

Kaplan Meier disease-free survival analysis for Age(A), and Weight loss (B)