

Weight loss improve pregnancy and livebirth outcomes in young women with early-stage endometrial cancer and atypical hyperplasia:15 years' experience

yanfang zhang

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital <https://orcid.org/0000-0003-3610-033X>

Dan Li

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Qi Yan

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Jinghua Wang

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

fei Teng

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Likun Wei

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

huiying zhang (✉ huiying_zhang2020@126.com)

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Wenyan Tian

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Yingmei Wang

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Xueru Song

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

Fengxia Xue

Tianjin Medical University First Clinical College: Tianjin Medical University General Hospital

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Abstract

Background: To evaluate the effects of body weight loss on pregnancy and livebirth outcomes in young women with early-stage endometrial cancer (EC) and atypical hyperplasia (AH) with fertility-sparing therapy. Thus, improve the management of this patient group.

Method: Patients with AH ($n=36$) and well-differentiated EC ($n=8$, FIGO stage IA) who achieved complete regression after conservative treatment were included in this retrospective study. A weight loss group ($n=25$) and a non-weight loss group ($n=19$) were divided; while subgroup analysis according to body mass index and stratification analysis according to weight loss proportion were performed to investigate the effect of weight loss on pregnancy and livebirth outcomes. A univariate and multivariate logistic regression analysis were undertaken to analysis the factors associated with pregnancy.

Results: The mean body weight and body mass index at pretreatment of progestin and initiation of fertility treatment was 70.63 ± 12.03 and 67.08 ± 8.18 kg, respectively, and 27.06 ± 4.44 and 25.73 ± 3.15 kg/m², respectively. 25 patients (56.82%) had weight loss; the median weight loss amount is 5.00kg (1.00-34.50), median weigh loss proportion was 6.70% (1.00-36.00) during median time interval of 12months (5.00-97.00). An impressive favorable pregnancy rate (65.91%) and live birth rate (50.00%) were achieved. The pregnancy and livebirth rate were meaningfully higher in the weight loss group than the non-weight loss group (88.00% vs.36.84%, $P=0.000$; 64.00% vs.31.58%, $P=0.033$, respectively); weight loss $\geq 5\%$ significantly increased pregnancy and live birth rate in patients with BMI ≥ 25 . The risk ratios of weight loss $\geq 5\%$ in multivariate logistic analysis for pregnancy was 0.096(0.010, 0.907).

Conclusions: Weight loss could have a positive effect on pregnancy rates and seem to be useful for improving live birth rates in overweight or obese women with early-stage endometrial cancer and atypical hyperplasia during/after fertility-sparing therapy. weight loss $\geq 5\%$ was protective factors of pregnancy in fertility-sparing patients with early-stage endometrial cancer and atypical hyperplasia.

1. Background

Endometrial carcinoma (EC) and its precursor atypical hyperplasia (AH) classically affect postmenopausal women. However, approximately 5% of cases of them occur in women aged 40 years or younger. The trend toward late childbearing has made fertility preservation a major issue for women who face EC and AH. Among the affected women, 70% are nulliparous[1]. NCCN guideline 2018 indicated fertility sparing management may be considered in selected patients and it is consistently recognized that progestin is safe and effective in conservative treatment[2]. Because the ultimate goal of fertility-sparing treatment is childbearing, following high dose progestin therapy and confirmation of the regression of cancer, a favorable pregnancy and livebirth rates in these patients are also clinical concerns. However, an unsatisfying pregnancy and livebirth rate reported recently in a systematic review and meta-analysis was 26.8% and 20.5%, respectively[3]. Meanwhile, few studies have evaluated the barriers to successful childbearing in these patients. It was known that obesity is a well-known disruptor of the female fertility but evidence is still lacking on whether weight loss interventions improve fertility in patients after fertility-sparing therapy. In the current study, we focused on such subset patients, aim to verify the importance of weight loss to improve pregnancy and livebirth outcomes and provide some procedures in clinical practice and management of those who require fertility-sparing treatment diagnosed with EC or AH.

2. Methods

This retrospective study included women younger than 40 years diagnosed with EC or AH who desired fertility-sparing management from May 2005 to May 2019.

Approval was obtained from the Institutional Ethics Committee.

All patients were given full information regarding the risks and benefits of conservative treatments, and all of the patients had signed consents.

Inclusion criteria:(1) histologically proven AH, or well-differentiated EC G1 without myometrial invasion on magnetic resonance imaging (MRI) (2) no signs of extrauterine involvement (3) strong desire to preserve fertility; (4) age ≤ 40 years old. (5) no contraindication for progestin treatment or pregnancy; (6) good compliance for treatment.

Exclusion criteria: (1) Lynch/hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (2) lost to follow up/data not extractable/ with unavailable data for body weight and height pretreatment of progestin and at imitation of fertility treatment (3) patients achieved complete regression (CR) did not wish to conceive immediately (4) women without a partner when the data was collected.

All patients were pathologically diagnosed by endometrial biopsy through dilation and curettage (D&C) with hysteroscopy.

Pathologic diagnosis was reviewed by two experienced gynecological pathologists according to the World Health Organization pathological classification (2014).

Medical records were reviewed for demographic, clinicopathological parameters, oncologic and reproductive data. Blood samples were tested for cancer antigen (CA125), 75g oral glucose tolerance test (OGTT), while fasting blood glucose (FBG), fasting insulin (FINS) for patients with diabetes mellitus. Homeostasis model assessment of insulin resistance (HOMA-IR) index $[FBG \text{ (mmol/L)} \times FINS \text{ (}\mu\text{U/mL)} / 22.5] \geq 2.69$ was defined as insulin resistance (IR). Body weights pretreatment (body weight1) of progestin and at initiation of fertility treatment (body weight2) were collected to get body weight change; body mass index (BMI) was calculated and marked as BMI1 and BMI2 respectively. Overweight was defined as $BMI \geq 25 \text{ kg/m}^2$. and Obesity as $BMI \geq 30 \text{ kg/m}^2$

Following confirmation of EC or AH, appropriately selected patients who desire fertility preservation were recommended to be referred to a reproductive endocrinologist to assess reproductive fertility. In overweight or obesity women, health education was performed and weight loss was recommended.

Patients received a daily oral dose of 250–500 mg medroxyprogesterone acetate (MPA) or 160mg-320mg megestrol acetate (MA). Metformin 1500 mg/day was administered concurrently for patients with insulin resistance. Metformin therapy was continued after progestin administration until conception. Endometrial biopsy through dilation and curettage (D&C) with hysteroscopy was performed once 3 months after initiating progestin administration. CR was defined as remission with the absence of evidence of hyperplasia or carcinoma. Progestin was continued to the second negative biopsy.

We recommended that the patients undergo infertility treatment as soon as possible after progestin withdrawal. The parameters, which included infertility management, endometrial thickness during ovulation or embryo transfer date, the clinical pregnancy and live-birth outcomes were collected. Clinical pregnancy was defined as observation of a gestational sac on a transvaginal ultrasound scan. Early pregnancy loss including loss of an intrauterine pregnancy < 12 weeks and biochemical pregnancy losses were included also in this study. Biochemical pregnancy was diagnosed as Human chorionic gonadotropin $\geq 25 \text{ mIU/mL}$. Endometrial thickness was measured via transvaginal ultrasound. Follow-up period was initiated from the date of progestin withdrawal. All patients were followed till December 2020. The median follow-up period was 86.80 months (12.00-188.50).

Study end-points: weight loss and pregnancy and livebirth outcomes

3. Results

3.1 Patient characteristics

A total of 36 AH and 8 EC patients who met inclusion criteria were enrolled in. The total patients' characteristics are summarized in Table 1. The median age at diagnosis was 32.00 years; the mean body weight1 and body weight2 was $70.63 \pm 12.03 \text{ kg}$ and $67.08 \pm 8.18 \text{ kg}$ respectively; the mean BMI1 and BMI2 was $27.06 \pm 4.44 \text{ kg/m}^2$ and $25.73 \pm 3.15 \text{ kg/m}^2$. 30(68.18%) and 23(52.27%) patients were overweight or obese respectively pre- and post-weight loss. 34(77.27%) patients were nulligravida and 42(95.45%) were nulliparity; 33(75.00%) patients were infertility; the average HOMA-IR was 4.70, 32(72.73%) patients were diagnosed with insulin resistance and treated with metformin. 23(52.30%) patients met the criteria for Polycystic ovarian syndrome (PCOS) (Rotterdam 2003 criteria). 9(20.45%) patients were diagnosed with hypertension and 6(13.64%) with diabetes mellitus. 25(56.82%) patients were administrated with MPA and 19(43.18%) with MA in conservative treatment.

3.2 Weight loss and reproductive outcomes

As shown in table 2, the median time interval between the two measurements of body weights was 12 months (range 5-97 months). 25 patients (56.82%) had weight loss, the median weight loss amount is 5.00kg (1.00-34.50), weight loss proportion was 6.70% (1.00-36.00). In the patients with $BMI \geq 25$ and $BMI < 25$ the median weight loss amount is 5.00kg (1.00-34.50) and 3.00(2.00-4.50) respectively, and weight loss proportion was 7.34%(1.00-36.00) and 5.17%(3.00-7.00) respectively. 12 patients (27.27%) had no weight change and 7 (15.91%) patients had weight gain, the median weight gain was 2.50kg (1.50-10.00), all of these 19 patients were regarded as non-weight loss group.

The pregnancy and livebirth rate were significantly increased in weight loss group than non-weight loss group in total 44 patients (88.00% vs.36.84%, $P=0.000$; 64.00% vs.31.58%, $P=0.033$, respectively) and patients with $BMI \geq 25$ (86.37% vs.12.50%, $P=0.000$; 59.09% vs.0.00%, $P=0.004$, respectively); In $BMI < 25$ patients, weight loss had no effects on pregnancy and livebirth outcomes ($P=0.05$). Weight loss was not associated with increased or decreased pregnancy loss ($P=0.05$).

As shown in table 3, in total patients, the pregnancy rate of patients with non-weight loss, weight loss $\geq 5\%$ and weight loss $\geq 5\%$ was 36.84%, 80.00% and 90%, respectively ($P=0.001$); 12.50%, 75.00% and 88.89% respectively in overweight and obese patients ($P=0.000$). Meanwhile, in total patients, the live birth rate of patients with non-weight loss, weight loss $\geq 5\%$ and weight loss $\geq 5\%$ was 31.58%, 60.00% and 65.00%, respectively ($P=0.118$); 0.00%, 50.00% and 61.11% respectively in overweight and obese patients ($P=0.010$).

Associated factors of pregnancy among patients after conservative treatment in univariate analysis shown in table 4. A 5% proportion of weight loss was independent protective factors for pregnancy adjusted as age at diagnoses, treatment time of progestin, and endometrial thickness, RR for pregnancy was 0.096(0.010, 0.907), detailed in table 5.

3.3 Reproductive outcomes and fertility treatment

Of 44 patients, 30 patients received the assistance of assisted reproductive technology (ART) and 14 patients attempted natural pregnancy (Non-ART). 29 patients got pregnancy in total. The pregnancy rate was 65.91% (29/44). 19/29(65.52%) patients got pregnancy by ART and 10/29(34.48%) spontaneously. It was demonstrated that the pregnancy rate was higher in natural conception patients than women undertaken ART therapy, although the difference was nonsignificant (71.43% vs.63.33%; $P=0.738$), and live birth rate was not different (50.00% vs.50.00%; $P=1.000$) between ART and Non-ART treatment. Of these 29 patients succeeded with 35 clinical pregnancies and 22 gave birth to 26 healthy babies (24 singletons and 1 twins; 23 full-term and 2 preterm livebirths; 17 girls and 9 boys; 3 patients had given birth twice). The live birth rate was 50.00% (22/44). There were 6 patients had early intrauterine pregnancy losses and 2 patients had biochemical pregnancy losses, 1 ectopic pregnancy and 1 stillbirth (32 weeks), 2 are still in pregnancy until the last follow up. Detailed in Figure 1.

3.4 Statistical analysis

All data were presented as means, medians, or proportions. The median values were compared using Mann-Whitney U-test. Frequency distributions were compared using the Chi-squared test or Fisher's exact test. Multivariate analysis was performed in the pregnancy and non-pregnancy groups using endometrial thickness, number of D&C, duration of progestin, age at diagnosis, hormone level and fasting plasma glucose as independent variables, using a logistic regression to determine the risk ratios. The difference was regarded as statistically significant when P -value ≤ 0.05 in two-sided test. All statistical analyses were performed using SPSS for Mac (version 23.0; IBM).

4. Discussion

The prevalence of obesity is increasing worldwide, with a corresponding increase in overweight and obese patients referred with infertility. It is well established that obesity is not only the leading risk factor in the development of endometrial cancer and its precancerous lesions; but also, as disruptor of the female fertility, it affects ovulation, oocyte development, maturation and quality, endometrial receptivity, implantation, and even miscarriage[4–6]. But little is known about the impact of weight loss on pregnancy rate and livebirth outcomes in EC and AH patients who received fertility-preserving treatment. In current study it was demonstrated an impressive favorable pregnancy rate (65.91%) and live birth rate (50.00%) after weight loss in fertility-sparing treatment women, which were meaningfully higher than those reported in literature[3, 7]. This study is the first to show that the pregnancy and livebirth rate were significantly higher in weight loss group than non-weight loss one among young women with early-stage endometrial cancer (EC) and atypical hyperplasia (AH).

With the intervention of weight loss, the current study indeed demonstrated more cases of natural pregnancies or pregnancies by ovulation induction occurring soon after conservative treatment, but not In vitro fertilization (IVF) pregnancies. Most of these women in present study suffered from infertility or subfertility with underlying disorders related to overweight/obesity and PCOS, which conditions should be encouraged to seek assisted reproductive therapy (ART) for conception. Studies reported that ART might increase the likelihood of pregnancy than spontaneous way (39.4% VS 14.9%) and decreases the interval to conception[3, 8, 9]. But in this study, Non-ART patients achieved the same, even more favorable reproductive outcomes compared to ART group, pregnancy rate (71.43% vs 63.33%; $P=0.738$) and live birth rate (50.00% vs 50.00%; $P=0.813$) respectively. Moreover, only 16 out of 44 patients (patients at advanced age, primary ovarian insufficiency diagnosed, failed to be pregnant by ovulation induction.) required the aid of IVF, and only 9 of the 16 patients who received IVF in the study successfully got pregnant. So far, limited studies, mainly case reports and retrospective studies, have investigated the association between controlled ovarian hyperstimulation and cancer risk, which mainly refer to endometrial and ovarian cancer risk, the conclusions were inconsistent across trials, our understanding is inconclusive given the short follow-up terms and lack of information on important confounders[10–12]. Outcomes in this study indicated that the benefits of weight reduction, including not only improvement in pregnancy rates, but also a reduced need for IVF. So, it is of paramount importance that overweight and obese women are given the necessary advice and support to achieve the weight loss before pregnancy during/after fertility-sparing treatment.

To date, only one research about the significance of weight change on pregnancy and livebirth outcomes in young EC women who undertook fertility preservation treatment is reported[13]. In this study, Park, J Y argued that pre and posttreatment of progestin, BMIs and weight

change were not associated with pregnancy and live birth rates, which is not completely consistent with our results. It was demonstrated in our study that (the data not shown) BMI at pretreatment of progestin and at pretreatment of infertility and weight gain were not associated with pregnancy and live birth rate (additional Table 1), but an improved pregnancy and livebirth outcomes were shown resulting from weight loss.

Firstly, the difference may come from the higher weight loss composition with weight loss interventions in our study, the proportion of weight loss (56.82%). In Park' study, without weight loss interventions mentioned, a lower weight loss (33.1%) and higher weight gain (48.1%) proportion were shown, the BMI posttreatment was higher than pretreatment, i.e., BMIs were 25.99 ± 5.94 and $25.51 \pm 5.99 \text{kg/m}^2$ ($P = 0.034$). Secondly, to accurately analyze the relationship between weight change and pregnancy and livebirth outcomes, a subgroup analysis according to BMI was done in current study, which was not included in Park'. A conclusion was drawn in subgroup analysis that weight loss meaningfully increased the pregnancy and livebirth rate, especially in overweight and obese patients ($\text{BMI} \geq 25$). Thirdly, a 5% weight loss proportion in ours according to perform stratification analysis was different from the 10% proportion which according to in Park' study.

It is unknown what is the differences of weight loss proportion on fertility in patients with EC and AH after conservative treatment. In obese women with PCOS only 2–5% of total body weight loss from baseline is generally accepted as a "clinically meaningful amount" to improve ovulatory function and is more likely to result in spontaneous pregnancy. There is also evidence to support improved outcomes from ovulatory cycles and pregnancy at moderate weight loss (5–10%) of total body weight loss[14]. Reported for the first time in current study, weight loss $\geq 5\%$ was associated with improved pregnancy and livebirth rate, and meanwhile was independent protective factors for pregnancy after adjust as age at diagnosis, duration of progestin, and endometrial thickness. But weight loss seemed not to associate with decreased pregnancy loss, this may lie in the small cases of this study and it also raises another consideration, what amount of weight loss is necessary to achieve benefit with respect to different medical purposes. Although there are few studies has been done to demonstrate whether it is true that the greater level weight loss the even greater improvement on female fertility, clinicians in medical weight management should bear in mind that the target should be reproductive health improvement, rather than a large number on the scale, different tissues and individual patients respond differently to weight loss. Moreover, consistent with literatures, it was demonstrated that in this study, overweight and obesity before pregnancy increased the pregnancy loss and decreased livebirth rate (data not shown)[15–17]; it was also shown in our data that weight loss was unrelated to an increased risk of pregnancy loss. So, in this sense weight loss is crucial and safe for the clinical management of this patient group.

Progestin therapy is a widely accepted, effective treatment for EC and AH, but paradoxically, weight gain is a well-known side effect[18]. In this study, weight gain was not

evident (15.91%) and made little influence on reproductive outcomes. Otherwise, most patients achieved weight loss, it perhaps mainly affected by administration of metformin. 72.73% women in our study commonly used metformin because of insulin resistance. Metformin has been examined in multiple disease processes as a weight gain prevention tool. Metformin appears to impact appetite regulation both directly and indirectly due to its gastrointestinal side effects and a modified microbiome to decreased caloric intake versus increases in energy expenditure[19]. Moreover, health education related non-pharmacological interventions may take some account of weight loss[20]. In overweight and obese patients in current study, health education was performed and the majority expressed interest in weight loss interventions in person; with a relatively long time to lose weight before pregnancy, 22 patients(73.3%) lost weight and 18 patients(60%) achieved $\geq 5\%$ proportion, which may improve outcomes from ovulatory cycles and pregnancy rate [20]. Just as Ashley F' study about relationship between obesity and endometrial cancer arguing that "a lack of knowledge but opportunity for intervention"[21].

The study demonstrated a significant high incidence of cesarean delivery (22 among 25 pregnancies; 88%) among women after conservative treatment. To some extent, the increased cesarean rate in these women appears to be associated with hypertensive disorders, macrosomia related to gestational diabetes mellitus which may be associated with a higher BMI pre and during pregnancy, A proper weight loss amount pre-pregnancy and weight gain during pregnancy are crucial to improve obstetric outcomes. Meanwhile with misconception on delivery mode among neoplastic disease survivor, social factors increased the incidence of cesarean delivery. So, caring for these young cancer patients requires collaboration between a dedicated, adherent patient and her medical team of gynecological oncologist, reproductive endocrinologist and obstetric experts.

With the primary limitation of retrospective analysis conducted at a single center and small cases of patients, further large-scale well-designed RCTs studies are necessary.

5. Conclusion

we have demonstrated weight loss may be an effective way to improve the pregnancy and livebirth outcomes in patients with early-stage endometrial cancer and atypical hyperplasia during/after fertility-sparing therapy, especially in overweighted or obese patients.

6. Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Tianjin Medical University General Hospital, and all the patients provided informed consent

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files)

Competing interests

All authors declare that they have no conflict of interest.

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Authors' contributions

Huiying Zhang, Wenyan Tian, Yingmei Wang, Xueru Song, Fengxia Xue: study design and execution; Yanfang Zhang, Dan Li: analysis and interpretation, manuscript preparation, and critical discussion; Qi Yan: data collection and literature retrieval; Jinghua Wang: Statistical analysis; Fei Teng, Likun Wei: assisted with design, data analysis, interpretation. All the authors examined the data and approved the final manuscript.

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Tables

Table 1 Patients basic characteristics

Parameters	Total patients (n=44)
Age at diagnosis(years)	32.00(25.00-40.00)
Endometrial cancer, <i>n</i> (%)	8(18.18)
Atypical hyperplasia, <i>n</i> (%)	36(81.82)
Infertility, <i>n</i> (%)	33(75.00)
nulligravida, <i>n</i> (%)	34(77.27)
Nulliparous, <i>n</i> (%)	42(95.45)
Homeostasis model assessment of insulin resistance index	4.70±3.33
Insulin resistance, <i>n</i> (%)	32(72.73)
Body weight1(kg)	70.63±12.03
Body weight2(kg)	67.08±8.18
Body mass index1(kg/m ²)	27.06±4.44
Body mass index2(kg/m ²)	25.73±3.15
Body mass index1≥25, <i>n</i> (%)	30(68.18)
Body mass index2≥25, <i>n</i> (%)	23(52.27)
Polycystic ovarian syndrome, <i>n</i> (%)	23(52.30)
Hypertension, <i>n</i> (%)	9(20.45)
Diabetes mellitus, <i>n</i> (%)	6(13.64)
Medroxyprogesterone acetate, <i>n</i> (%)	25(56.82)
Megestrol acetate, <i>n</i> (%)	19(43.18)

Body weight1 and Body mass index1: Body weight and BMI at pretreatment of progestin

Body weight2 and Body mass index2: Body weight and BMI at imitation of infertility

Table 2 Weight loss and reproductive outcomes

	Total patients (n=44)			BMI1≥25(n=30)			BMI1<25(n=14)		
	weight loss (n=25)	non-weight loss (n=19)	P value	weight loss (n=22)	non-weight loss (n=8)	P value	weight loss (n=3)	non-weight loss (n=11)	P value
Body weight1(kg)	76.26±11.37	63.21±8.46	-	78.23±10.56	71.50±5.71	-	61.83±5.01	57.18±3.35	-
Body weight2(kg)	68.94±8.20	64.63±7.69	-	70.34±3.62	72.00±5.89	-	58.67±4.04	59.27±2.67	-
BMI1(kg/m ²)	29.02±4.07	24.48±3.55	-	29.83±3.63	27.84±2.64	-	23.09±0.77	22.03±1.47	-
BMI2(kg/m ²)	26.28±3.09	25.01±3.18	-	26.83±2.67	28.03±2.60	-	22.24±0.36	22.83±0.99	-
Weight loss amounts(kg)	5.00(0.50-34.50)	-	-	5.00(0.50-34.50)	-	-	3.00(2.00-4.50)	-	-
Weigh loss ratios (%)	6.70(1.00-36.00)	-	-	7.34(1.00-36.00)	-	-	5.17(3.00-7.00)	-	-
BMI change(kg/m ²)	1.82(0.18-12.37)	-	-	2.16(0.18-12.37)	-	-	0.77(0.21-1.57)	-	-
Time interval(months)	12.00(5.00-97.00)	-	-	-	-	-	-	-	-
Pregnancy n (%)	22(88.00)	7(36.84)	0.000	19(86.37)	1(12.50)	0.000	3(100.00)	6(54.55)	0.258
Live birth n (%)	16(64.00)	6(31.58)	0.033	13(59.09)	0	0.004	3(100.00)	6(54.55)	0.580
Pregnancy loss n (%) ^a	7(29.17) ^b	1(14.29)	0.642	7(33.33) ^c	1(100.00)	0.364	0	0	-

Weight loss group=patients had weight reduction; Non-weight loss group=patients had no weight change and patients had weight gain. Body weight1 and BMI1: Body weight and BMI at pretreatment of progestin; Body weight2 and BMI2: Body weight and BMI at imitation of infertility

a: pregnancy loss including 6 early intrauterine pregnancy losses and 2 biochemical pregnancy losses; b:7/24=29.17%,24=22 patients got clinical pregnancy and 2 patients diagnosed as biochemical pregnancy; c:7/21=33.33%,21=19 patients got clinical pregnancy and 2 patients diagnosed as biochemical pregnancy

Table 3 Body weight loss proportion and pregnancy and live birth outcome

	Total patients (n=44)				BMI1≥25(n=30)			
	Non-weight loss (n=19)	weight loss 5% (n=5)	Weight loss≥5% (n=20)	P value	Non-weight loss (n=8)	weight loss 5% (n=4)	Weight loss≥5% (n=18)	P value
Pregnancy n (%)	7(36.84)	4(80.00)	18(90.00)	0.001	1(12.50)	3(75.00)	16(88.89)	0.000
Live birth n (%)	6(31.58)	3(60.00)	13(65.00)	0.118	0	2(50.00)	11(61.11)	0.010

BMI1: BMI at pretreatment of progestin

Table 4. Associated factors of pregnancy among patients after conservative treatment in univariate analysis

Category	Pregnancy	Non-pregnancy	P
Age at diagnosis, <i>mean±SD</i> (years)	30.72 (4.18)	33.4 (2.56)	0.033
duration of progestin, <i>mean±SD</i> (months)	5.93 (1.19)	8.07 (2.71)	<0.001
Weight change value, <i>mean±SD</i> (kg)	-4.83 (8.26)	-1.37 (4.28)	0.024
FBG, <i>mean±SD</i> (mmol/L)	5.46 (0.85)	5.49 (1.05)	0.069
number of D&C, <i>mean±SD</i> (times)	4.48 (1.27)	7.13 (3.04)	0.014
Endometrial thickness, <i>mean±SD</i> (mm)	9.39 (1.34)	7.46 (1.8)	<0.001

Mann-Whitney U test

number of D&C: number of dilation and curettage

Table 5. Risk ratios (RR) for pregnancy using logistic regression analysis

Category	Reference	Univariate analysis			multivariate analysis		
		RR	95% CI	Pvalue	RR	95% CI	Pvalue
Weight loss ratios	non-weight loss						
Weight loss<math>\leq 5\%		0.146	(0.013, 1.578)	0.113	0.060	(0.001, 2.665)	0.177
Weight loss $\geq 5\%$		0.065	(0.011, 0.367)	0.002	0.096	(0.010, 0.907)	0.041

Multivariate analysis adjusted as age at diagnosis, duration of progestin, and endometrial thickness

Additional table 1 BMIs and Weight gain and reproductive outcomes

		Pregnancy <i>n</i> (%)			Pregnancy loss <i>n</i> (%) ^a			Live birth <i>n</i> (%)		
		Yes (29)	No (15)	Pvalue	Yes (8)	No (23)	Pvalue	Yes (22)	No (22)	Pvalue
Total (<i>n</i> =44)	BMI1 ≥ 25 (<i>n</i> =30)	20(66.67)	10(33.33)	1.000	8(36.36)	14(63.64)	0.068	13(43.33)	17(56.67)	0.195
	≤ 25 (<i>n</i> =14)	9(64.29)	5(35.71)		0	9(100.00)		9(64.29)	5(35.71)	
	BMI2 ≥ 25 (<i>n</i> =23)	13(56.52)	10(43.48)	0.169	7(46.67)	8(53.33)	0.015	8(34.78)	15(65.22)	0.035
	≤ 25 (<i>n</i> =21)	16(76.19)	5(22.81)		1(6.25)	15(93.75)		14(66.67)	7(33.33)	
	Weight gain yes (<i>n</i> =7)	5(71.43)	2(28.57)	1.000	1(20.00)	4(80.00)	1.000	4(57.14)	3(42.86)	1.000
	no (<i>n</i> =37)	24(64.86)	13(35.14)		7(26.92)	19(73.08)		18(48.65)	19(51.35)	
BMI ≥ 25 (<i>n</i> =30)	Weight gain yes (<i>n</i> =2)	1(50.00)	1(50.00)	1.000	1(100.00)	0	0.364	0	2(100.00)	0.492
	no (<i>n</i> =28)	19(67.86)	9(32.14)		7(33.33)	14(66.67)		13(46.43)	15(53.57)	
BMI ≤ 25 (<i>n</i> =14)	Weight gain yes (<i>n</i> =5)	4(80.00)	1(20.00)	0.580	0	4(100.00)	-	4(80.00)	1(20.00)	0.580
	no (<i>n</i> =9)	5(55.56)	4(44.44)		0	5(100.00)		5(55.56)	4(44.44)	

Weight gain: yes=patients with weight gain; no=patients with no body change and patients with weight loss; BMI1: BMI at pretreatment of progestin; BMI2: BMI at initiation of fertility treatment;

^a: pregnancy loss including 6 early intrauterine pregnancy losses and 2 biochemical pregnancy losses

Figures

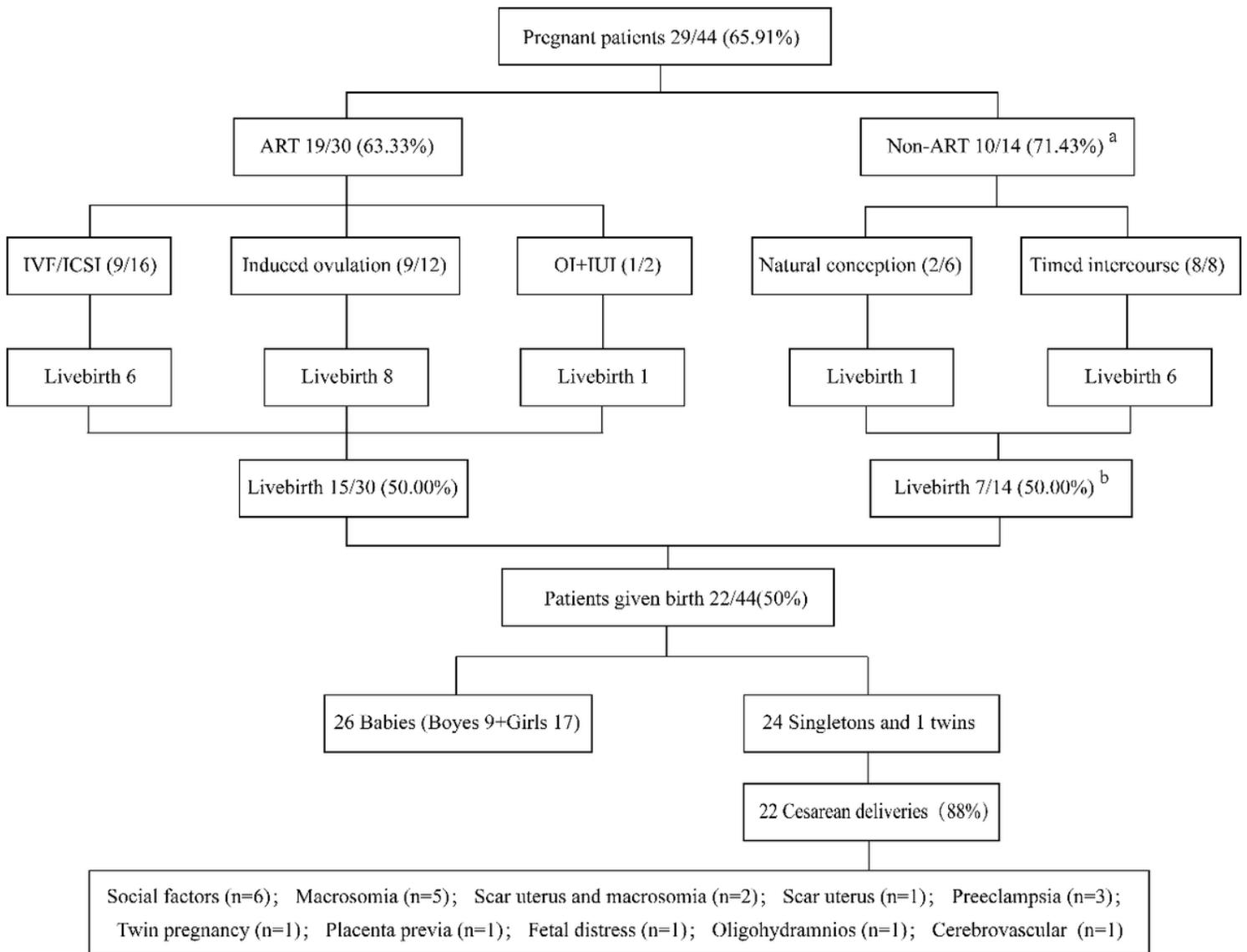


Figure 1

Infertility treatment after conservative treatment and reproductive outcomes. ART: assisted reproductive therapy; IVF: In vitro fertilization; ICSI: Intracytoplasmic Sperm Injection; OI: ovulation induction; IUI: Intrauterine insemination a: the pregnancy rate of Non-ART patients was not different from the ART patients (P=0.738); b: the livebirth rate of Non-ART patients was same as the ART patients (P=1.000).