Efficacy of Natural Cycle versus GnRH-a Down Regulation Cycle of Endometrial Preparation in Minimal and Mild endometriosis Patients Undergoing Frozen-Thawed Embryo Transfer

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Research article

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Abstract

Background Minimal and mild endometriosis patients with infertility are treated by in vitro fertilization and embryo transfer/intracytoplasmic sperm injection (IVF-ET/ICSI) in recent years. However, inconsistencies in findings within and across individual studies raise concerns as to determine which method is the best treatment, especially in the frozen-thawed embryo transfer cycle (FET). We hope to compare the efficacy of natural cycle versus GnRH-a down regulation cycle endometrial preparations in minimal and mild endometriosis patients undergoing FET.

Methods We retrospectively analyzed a cohort of 1170 minimal and mild endometriosis patients receiving FET at the Reproductive Medicine Centre from Chengdu Jinjiang Hospital for Maternal and Child Health Care from January 1, 2016 to December 31, 2018. They were assigned to the natural cycle group and the GnRH-a down regulation cycle group based on endometrial preparation protocols. Baseline characteristics, frozen-thawed embryo transfer cycle and pregnancy outcomes were compared between the two groups.

Results There were nonsignificant differences in baseline characteristics including age, BMI, types of infertility, the duration of infertility and the delivery history between the natural cycle group and the GnRH-a down regulation cycle group ($P>0.05$). The biochemical pregnancy rate (63.62% *v.s.* 53.83%), clinical pregnancy rate (56.10% *v.s.* 47.49%), implantation rate (43.19% *v.s.* 34.88%) and live birth rate (44.31% *v.s.* 35.84%) in the natural cycle group were significantly higher than those in the GnRH-a down regulation cycle group ($P<0.05$). However, there were nonsignificant differences in the multiple birth rate, abortion rate, ectopic pregnancy rate, premature birth rate, neonatal weight and length between the two groups ($P>0.05$). The multivariate regression analysis showed that age, anti-Müllerian hormone (AMH), the number of transplanted high-quality blastocysts and endometrial preparation protocols were associated with the live birth rate in minimal and mild endometriosis women undergoing FET ($P<0.05$).

Conclusion Compared with GnRH-a down regulation cycle, natural cycle endometrial preparation of FET is a prominent endometrial preparation method for improving the implantation rate, clinical pregnancy rate, and live birth rate in minimal and mild endometriosis patients, which is more cost-effective in clinical practice.

Background

Endometriosis is a benign chronic gynecological disease featuring chronic pelvic pain and infertility in reproductive-age females, associated with the pathogenesis of the implantation of the endometrium outside the uterine cavity[1]. While the prevalence of endometriosis in women of childbearing age is about 10–15%, those with minimal and mild endometriosis combined with infertility comprise 25–50% of all endometriosis cases[2]. In a cohort study recruiting childbearing-age women with endometriosis, women younger than 35 years of age doubled the risk of infertility compared with those without endometriosis[3]. According to the American Society for Reproductive Medicine Stage (ASRM) score, endometriosis can be

classified as minimal (I), mild (II), moderate (III) and severe (IV)[4], and the incidence of minimal to mild minimal and mild endometriosis is much higher than that of moderate and severe endometriosis. Though the exact pathogenesis of infertility in patients with minimal or mild endometriosis has not yet been fully explored, it may attribute to anatomical changes in the pelvis, ovarian dysfunction, pelvic micro environment and inflammatory factors or cytokines that influence endometrial receptivity and egg / embryo quality[5–7].

In recent years, *in vitro* fertilization and embryo transfer/intracytoplasmic sperm injection (IVF-ET/ICSI) has been applied for minimal and mild endometriosis patients combined with infertility, especially for those who are still not pregnant undergoing surgery. However, previous studies about the efficacy of IVF-ET/ICSI in minimal and mild endometriosis women have yielded inconsistent results[8]. A meta-analysis uncovered that the diminished pregnancy rate, ovarian response, implantation rate and clinical pregnancy rate following IVF in endometriosis patients combined with infertility compared with infertile women due to fallopian tubal factors, which may attribute to decreased endometrial receptivity and damaged mitochondrial structure and function in oocytes in minimal and mild endometriosis[9]. However, another relevant study only reported non-significant differences in pregnancy outcomes between endometriosis patients combined with infertility and infertile women due to fallopian tubal factors after IVF-ET/ICSI[10], which is supported by another meta-analysis conducted in 2015 that there are similar pregnancy outcomes between endometriosis patients and pregnant women without severe diseases[11]. Compared with fresh embryo transfer during controlled ovarian hyperstimulation (COH), FET contributes to an improved cumulative clinical pregnancy rate and persistent pregnancy rate in minimal and mild endometriosis patients as it minimizes the influence of high-level estrogen on endometrial receptivity during controlled ovarian hyperstimulation[12]. Although current studies emphasizing the optimal endometrial preparation protocols for minimal and mild endometriosis patients receiving FET have not reached a consensus[13, 14], GnRH-a down regulation and natural cycle of endometrial preparation in FETs are still the two major endometrial preparation methods for minimal and mild endometriosis patients. Numerous evidences show that GnRH-a could be able to decrease the influence of minimal and mild endometriosis on adverse pregnancy outcomes and to improve endometrial receptivity[15], and that down regulated FET using long-term GnRH-a might improve pregnancy outcomes, despite a concern for probability of resultant implantation failure owing to adverse reactions of exogenous hormones and inappropriate endometrial thickness[10]. As natural cycle endometrial preparation of FET does not require exogenous hormones, the natural physiological status of the endometrium can be largely preserved with merely a negligible influence [16].

Current studies about the influences of down regulation cycle and natural cycle of endometrial preparation in FETs on clinical outcomes of minimal and mild endometriosis women are rarely reported. So the aim of this study was to retrospectively analyze possible influences of the two main endometrial preparation protocols for minimal and mild endometriosis.

Methods

1.1 Subjects

Medical records of 1170 minimal and mild endometriosis patients undergoing FET in the Reproductive Medicine Centre from Chengdu Jinjiang Hospital for Maternal and Child Health Care from January 1, 2016 to December 31, 2018 were retrospectively analyzed. Minimal and mild endometriosis was pathologically confirmed after laparoscopic or open surgery. Patients were assigned to the natural cycle group and the GnRH-a down regulation cycle group according to specific endometrial preparation protocols. Subjects were included if (*i*) they were diagnosed as ASRM I-II after laparoscopic or open surgery; (*ii*) aged 20–40 years; and (*iii*) they received blastocyst transfer. Subjects were excluded if (*i*) infertility was caused by other factors; (*ii*) chromosomal abnormalities were found in one or both spouses; (*iii*) patients reported other endocrine diseases; (iv) they reported organic diseases of the uterus (e.g., adenomyosis, scar uterus and intrauterine adhesions); (*v*) malformation of the reproductive system was detected; or (*vi*) the spouse reported severe oligoasthenospermia, asthenospermia and teratozoospermia. c were compared between the two groups. The eligibility flow chart was depicted in Fig. 1.

The study was approved by the institutional research ethics committee of Chengdu Jinjiang Hospital for Maternal and Child Health Care, and written informed consent was obtained from each subject.

1.2 Methods

1.2.1 Endometrial preparation protocols

Transvaginal ultrasonography was performed and basal hormone levels were determined on day 2 or day 3 of the menstrual cycle for all patients. For women in the natural cycle group, the follicular size, endometrial thickness, the morphology of the endometrium and endometrial blood flow were monitored by transvaginal ultrasonography on day 8 to day 10 of the menstrual cycle. Serum levels of estradiol (E2), progesterone (P) and luteinizing hormone (LH) were detected once the dominant follicle size was up to 18–20 mm, and patients were administered by intramuscular injection of 6,000 U human chorionic gonadotropin (HCG; LIVZON, China) on the same day. After ascertaining the time of ovulation, they received the oral administration of dydrogesterone 20 mg bid (Abbott, Holland). Blastocyst thawed and transplanted were performed on day 5 of dydrogesterone administration.

For women in the GnRH-a down regulation cycle group, they accepted the intramuscular administration of 3.75 mg diphereline (Ipsen, France) on day 2 or day 3 of the menstrual cycle, and the endometrium was monitored by vaginal ultrasonography and basal hormone levels were re-examined on day 28th. For patients with E2 < 40 pg/ml, LH < 10mIU/mL, FSH < 10mIU/mL, endometrium < 5 mm on day 28th during GnRH-a down regulation cycles, endometrial preparation was undertaken with the oral administration of Femoston (red) 1 pill tid (Abbott, Holland) for 12 days. The levels of E2 and P in serum were determined, and the thickness and blood flow of the endometrium was detected by transvaginal ultrasonography on the 13th day. On the same day, subjects also received the oral administration of Femoston (yellow) 2 pills

bid (Abbott, Holland) and the vaginal administration of Crinone 90 mg qd (MERCK SEROND, Germany) if their endometrial condition was suitable for FET. Blastocysts thawed and transplanted were performed on day 5 of the oral and vaginal administrations. Estrogens could be supplemented (controlled in 20 days) if the endometrium was not appropriate. The funding from the Sichuan Science and Technology Program played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

1.2.2 Blastocyst frozen-thawed embryo transfer

The quality of embryos was rated based on the Gardner system[17]. frozen-thawed embryo transfer of blastocyst were performed in accordance with standard process. Based on the patients' conditions, 1–2 cultured blastocysts was/were transferred and guided by the vaginal ultrasound. Dydrogesterone and/or Crinone was administrated for luteal phase support.

1.2.3 Luteal-phase support and pregnancy confirmation

Medications for luteal-phase support were given continuously after blastocyst transplantation. On day 14th after transplantation, biochemical pregnancy was positive if the serum level of HCG was more than 25 U/L, while clinical pregnancy was confirmed with the presence of the gestational sac using transvaginal ultrasound on day 28th and day 38th after transplantation. Medications for luteal-phase support were given until 10–12 weeks of gestation.

1.3 Measurements

Baseline clinical and demographic characteristics of both groups were recorded, encompassing age, the duration of infertility, types of infertility, body mass index (BMI), antral follicle count (AFC), Anti-mullerian hormone (AMH), the number of transplanted blastocysts and the number of transplanted high-quality blastocysts. Clinical pregnancy outcomes consisted of the biochemical pregnancy rate (the percentage of subjects with a serum HCG level > 25 U/L on day 14 after transplantation in all transplanted subjects), the clinical pregnancy rate (the proportion of subjects with the presence of the gestation sac in all transplanted subjects), the implantation rate (the proportion of the number of the gestation sac in all transplanted blastocysts), the multiple pregnancy rate(the proportion of the subjects of the multiple gestation sacs in all subjects of clinical pregnancy), the miscarriage rate (the percentage of women with miscarriage in all subjects of clinical pregnancy), the ectopic pregnancy rate (the proportion of women with ectopic pregnancy in all subjects of clinical pregnancy), the live birth rate (the percentage of women giving birth to live-born infants in all transplanted subjects), the normal delivery rate (the percentage of women with normal vaginal delivery in all pregnant subjects), the cesarean section rate (the percentage of women with cesarean section in all pregnant subjects), newborn birth weight and length.

1.4 Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 software (IBM SPSS). Measurement data were expressed as $\bar{x}$±s. Differences between the two groups were compared using the independent *t* test if the data were normally distributed; otherwise, the Mann-Whitney *U* test was employed. Results of clinical pregnancy outcomes of the two groups were expressed as percentages, and compared using the Chi-square test or Fisher's exact test. Multivariate regression analysis was employed to assess influences of age, BMI, the duration of infertility, types of infertility, AMH, AFC, the number of transplanted blastocysts, the number of transplanted high-quality blastocysts, endometrial thickness on the day of transplantation and endometrial preparation protocols on the live birth rate of minimal and mild endometriosis patients. A *P* value < 0.05 was considered as statistically significant.

Results

2.1 Baseline characteristics of minimal and mild endometriosis women in natural cycle group v.s. GnRH-a down regulation cycle groups

A total of 1170 eligible subjects in their FET cycles were recruited, consisting of 492 subjects in the natural cycle group and 678 in the GnRH-a down regulation cycle group. No significant differences in age, the duration of infertility, types of infertility, BMI, delivery history and endometrial thickness on the day of transplantation were found between the two groups ($P > 0.05$). However, the AFC and AMH levels in the natural cycle group were significantly higher than those in the GnRH-a down regulation cycle group, while the numbers of transplanted blastocysts and transplanted high-quality blastocysts were lower in the natural cycle group ($P < 0.05$) (Table 1).

Table 1
Baseline characteristics of minimal and mild endometriosis women in natural cycle group *v.s.* GnRH-a down regulation cycle group

	Natural cycle group	GnRH-a down regulation cycle group	*P* value
FET cycles	492	678	
Age (years)			0.951
< 35	312 (63.41%)	428 (63.17%)	
≥ 35	180 (36.59%)	250 (36.87%)	
BMI (kg/m^2)	22.68 ± 3.22	22.88 ± 3.73	0.567
Duration of infertility	3.42 ± 2.22	3.52 ± 2.43	0.466
Types of infertility			0.814
Primary infertility	155 (31.50%)	218 (32.15%)	
Secondary infertility	337 (68.50%)	460 (67.85%)	
AMH	3.71 ± 3.01	3.11 ± 3.73	**0.006**
AFC	11.73 ± 6.48	9.57 ± 7.29	**< 0.001**
Delivery history			0.455
None	411 (83.54%)	555 (81.86%)	
Yes	81 (16.46%)	123 (18.14%)	
Number of transplanted blastocysts	1.72 ± 0.45	1.78 ± 0.42	**0.028**
Number of transplanted high-quality blastocysts	1.34 ± 0.66	1.60 ± 0.49	**< 0.001**
Endometrial thickness on the day of transplantation	10.00 ± 1.86	10.03 ± 1.79	0.820

2.2 Better Pregnancy Outcomes In Natural Cycle Of Fet

The biochemical pregnancy rate, clinical pregnancy rate, implantation rate and live birth rate were significantly higher in the natural cycle group than those in the GnRH-a down regulation cycle group ($P < 0.05$). There were nonsignificant differences in the multiple pregnancy rate, miscarriage rate, ectopic pregnancy rate, premature birth rate, normal delivery rate and cesarean section rate between the two groups, neither was newborn birth weight nor newborn birth length between the two groups ($P > 0.05$) (Table 2). There were no birth defects in both groups.

Table 2
Pregnancy outcomes of minimal and mild endometriosis women in natural cycle group *v.s.* GnRH-a down regulation cycle groups

	Natural cycle group	GnRH-a down regulation cycle group	*P* value
FET cycles	492	678	
Biochemical pregnancy rate	313 (63.62%)	365 (53.83%)	**< 0.001**
Clinical pregnancy rate	276 (56.10%)	322 (47.49%)	**0.004**
Implantation rate	43.19%	34.88%	**< 0.001**
Multiple pregnancy rate	62 (28.44%)	51 (20.99%)	0.063
Miscarriage rate	46 (16.67%)	58 (18.01%)	0.942
Ectopic pregnancy rate	3 (1.09%)	8 (2.48%)	0.238
Live birth rate	218 (44.31%)	243 (35.84%)	**0.003**
Premature birth rate	55 (25.23%)	73 (30.04%)	0.249
Normal delivery rate	20 (9.48%)	14 (5.81%)	0.14
Cesarean section rate	191 (90.52%)	227 (94.19%)	0.14
Newborn birth weight	2.82 ± 0.63	2.85 ± 0.63	0.515
Newborn birth length	48.13 ± 2.79	48.35 ± 2.65	0.382

2.3 Potential factors influencing the live birth rate in minimal and mild endometriosis women undergoing FET

Age, AMH, the number of transplanted high-quality blastocysts and endometrial preparation protocols were significantly associated with the live birth rate in minimal and mild endometriosis subjects undergoing FET ($P < 0.05$). However, BMI, the duration of infertility, types of infertility, AFC, the number of transplanted blastocysts and endometrial thickness on the day of transplantation were not associated with the live birth rate following FET ($P > 0.05$) (Table 3).

Table 3
Potential factors affecting live birth rate outcomes in minimal and mild endometriosis women undergoing FET

Potential factors	OR	95%CI	*P* value
Age (years)	0.92	(0.89, 0.94)	**< 0.001**
BMI (kg/m^2)	0.99	(0.95, 1.03)	0.634
Duration of infertility	1.01	(0.95, 1.07)	0.820
Types of infertility			0.089
Primary infertility	1		
Secondary infertility	1.30	(0.96, 1.76)	
AMH	1.08	(1.01, 1.14)	**0.014**
AFC	1.01	(0.98, 1.03)	0.640
Number of transplanted blastocysts	1.24	(0.84, 1.83)	0.280
Number of transplanted high-quality blastocysts	2.59	(1.98, 3.38)	**< 0.001**
Endometrial thickness on the day of transplantation	1.00	(0.93, 1.08)	0.905
FET cycles			**0.025**
Natural cycle endometrial preparation	1		
GnRH-a down regulation cycle endometrial preparation	0.71	(0.53, 0.96)	

Discussion

Endometriosis is an estrogen dependent inflammatory disease classically characterized by infertility and secondary progressively dysmenorrhea, which is becoming more prevalent in childbearing-age women. Endometriosis is closely related to infertility, about 10–25% of women with endometriosis have undergone IVF/ICSI[18], however whether minimal and mild endometriosis are associated with infertility and the outcomes of IVF/ICSI are still unclear. So more assisted reproductive technology for effectively improving the pregnancy rate for minimal and mild endometrios women are still needed. Though previous studies about the two major endometrial preparation protocols analyzed the correlations between fresh embryo transfer or FET and pregnancy outcomes in the population, their results are inconsistent. Therefore, in this study we aimed to compare the effects of natural cycle endometrial preparation versus long-term GnRH-a down regulation cycle endometrial preparation of FET on the live birth rate in minimal and mild endometriosis women.

In this study, all subjects were pathologically confirmed as I-II endometriosis of ASRM after laparoscopic or open surgery, and they were assigned to the natural cycle and GnRH-a down regulation cycle groups

according to specific endometrial preparation protocols. Their baseline characteristics were comparable. The biochemical pregnancy rate, clinical pregnancy rate, implantation rate and live birth rate were significantly higher in the natural cycle group than those in the GnRH-a down regulation cycle group. Besides, there were nonsignificant differences in the multiple pregnancy rate, miscarriage rate, ectopic pregnancy rate, premature birth rate, normal delivery rate and cesarean section rate between the two groups. By contrast, van de Houwen LE et al.[19] concluded that GnRH-a down regulation cycle of FET improved ongoing pregnancy rates compared with natural cycle of FET in severe endometriosis patients. However,another study has assessed the influence of endometrial peristalsis on embyros/blastocysts implantation and has reported that natural cycle of FET is instrumental to a high pregnancy rate[20]. Nevertheless, they did not take into consideration different endometrial preparations. Levron et al. demonstrated that the implantation rate and clinical pregnancy rate were improved after natural cycle of FET, which is consistent with our findings. In addition, in long-term GnRH-a down regulation cycle, minimal and mild endometriosis patients in the present study were supplemented with exogenous estrogens before the placental function was established. Due to no using of exogenous estrogens, natural cycle of FET do not alter endometrial receptivity, and there were a more natural effect of luteal support for blatocyst development; moreover, it is cost-saving during a short period of treatment.

Embryo quality and endometrial receptivity are the major factors that influence outcomes following FET. In our study, both blastocyst culture and cryopreservation during the controlled ovarian hyperstimulation cycle contribute to a high pregnancy rate and live birth rate after FET. To obtain higher developmental potential[21], we eliminated blastocysts with poor quality or chromosomal abnormalities, and we kept high-quality blastocysts during blastocyst culture, and then performed the vitrification for good quality blastocysts. And we discover that more high-quality transplanted blastocysts is what matters to a higher live birth rate after FET, rather than the number of transplanted blastocysts, which is also supported by the study by Bourdon M et al.[22]

In the present study we confirmed that age and AMH levels were associated with the live birth rate following FET. Evidences show that age is an independent risk for the live birth rate. With the increasing age, diminished quality of oocytes alongside mitochondrial dysfunction and oxidative stress increases the risk of embryo chromosome abnormalities, often manifesting as the presence of aneuploid embryo and a low blastulation rate[23]. Decreases in AMH levels and the AFC indicate a reduced ovarian reserve, which further influences the numbers of eggs, embryos and high-quality embryos.

It is reported that minimal and mild endometriosis may have a certain impact on low newborn birth weight[24]. Although no significant differences in newborn birth weight and length were identified between the natural cycle and GnRH-a down regulation cycle groups, a higher premature rate and lower newborn birth weight in both groups were consistent with previous studies[19, 25]. As a result, further research is required to clarify the correlation between minimal and mild endometriosis and low newborn birth weight. It is reported that IVF treatment in severe minimal and mild endometriosis patients may enhance susceptibilities to congenital cardiovascular and skeletal muscle diseases in neonates[26]. After we

screened fetal malformation, although there were early and late abortions in both groups during pregnancy, no birth defects were detected, which can be explained by the inclusion of minimal and mild endometriosis patients, high-quality blastocysts transplantation, comprehensive prenatal examinations of the abnormal fetus, or a small sample size.

This is a retrospective non-randomized controlled trial, so a potential selection bias may influence the research quality. A prospective randomized controlled trial at multi-centers is required to validate our findings. Summarily, this study demonstrates that natural cycle endometrial preparation is superior to GnRH-a down regulation cycle endometrial preparation in terms of the implantation rate, clinical pregnancy rate and live birth rate, which also improves the cost-effectiveness of FET for women with minimal and mild endometriosis. A large sample size is still required to re-verify the influence of endometrial preparations on pregnancy outcomes of Chinese minimal and mild endometriosis women undergoing FET.

Abbreviations

FET: frozen-thawed embryo transfer; IVF-ET/ICSI: *in vitro* fertilization and embryo transfer/intracytoplasmic sperm injection; COH: controlled ovarian hyperstimulation; GnRH-a: gonadotropin-releasing hormone agonist; AMH: anti-Müllerian hormone; AFC: antral follicle count.

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the institutional research ethics committee of Chengdu Jinjiang Hospital for Maternal and Child Health Care. Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Availability of Data and Materials: The data that support the findings of this study are available from the Reproductive Medicine Centre from Chengdu Jinjiang Hospital for Maternal and Child Health Care but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Reproductive Medicine Centre from Chengdu Jinjiang Hospital for Maternal and Child Health Care.

Competing interests: The authors have no competing interests to declare.

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Authors' contributions: YL and JZ were responsible for the study inception and design. YL and LW performed the data extraction. YL, ST and YZ interpreted the data, and YL wrote the manuscript. All authors have read, critiqued and approved the final manuscript.

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Figures

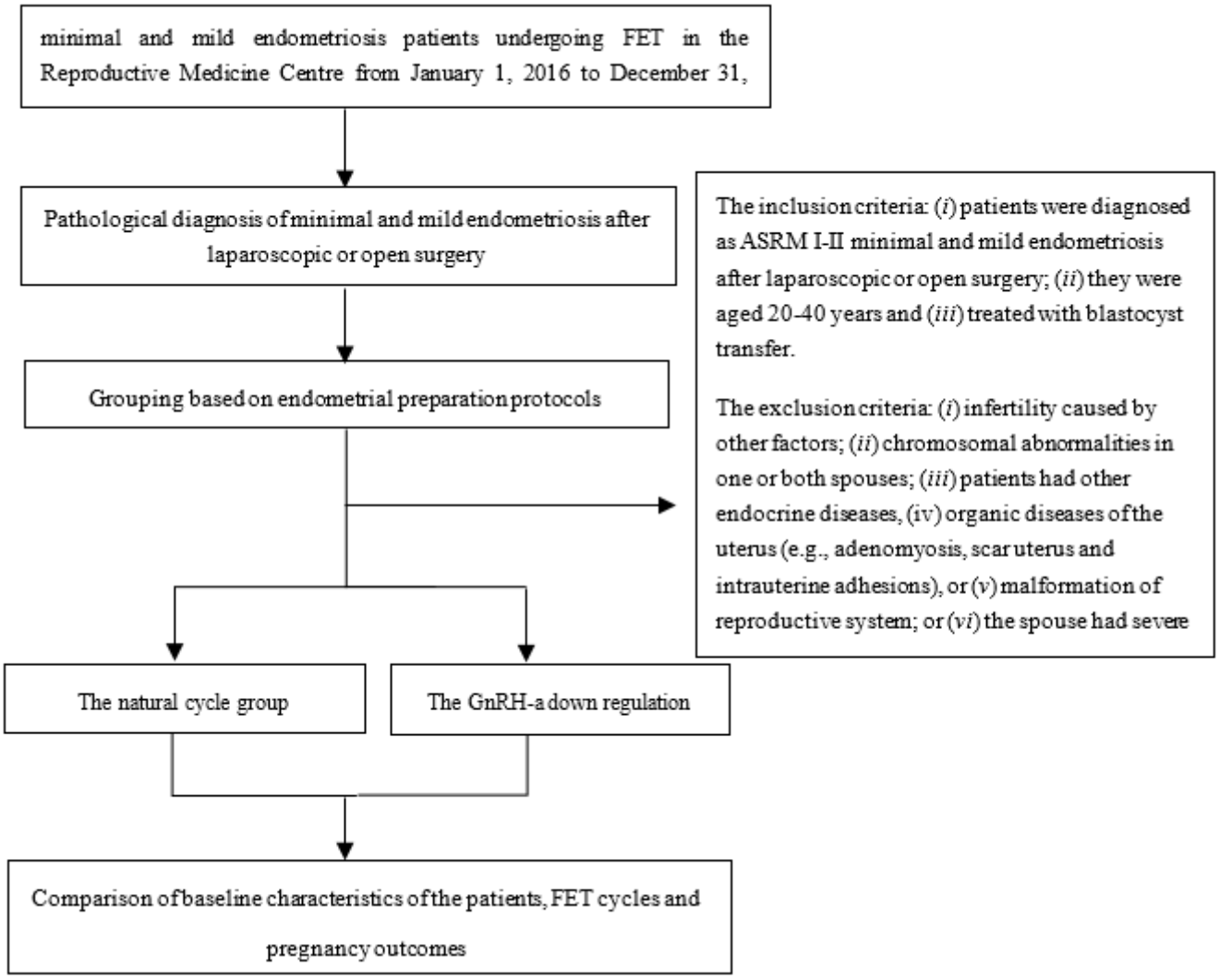

Figure 1

The eligibility flowchart of subjects in this study