Fixed Versus Flexible Antagonist Protocol in Women with Predicted High Ovarian Response except PCOS : A Randomized Controlled Trial

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Abstract

Background: No previous study directly compares the fixed day-5 initiation versus the flexible initiation of GnRH antagonist administration in IVF/ICSI for those patients who are predicted as high ovarian responders without PCOS. To evaluate whether the number of oocytes retrieved is different by using the two GnRH antagonist protocols in Chinese women with predicted high ovarian response except PCOS.

Methods: A randomized controlled trial of 201 infertile women with predicted high ovarian response except PCOS undergoing in vitro fertilization. Ovary stimulation was performed using recombinant FSH and GnRH antagonists. GnRH antagonist ganirelix (0.25 mg/d) was started either on day 5 of stimulation (fixed group) or when LH was >10 IU/L, and/or a follicle with mean diameter >12 mm was present, and/or serum E2 was >300pg/ml. Patient monitoring was initiated on day 3 of stimulation in flexible group.

Result(s): No significant difference was observed between the fixed and flexible groups regarding the number of oocyte retrieved(16.72±7.25 vs. 17.47±5.88, *P*=0.421), the Gonadotropin treatment duration(9.53±1.07 vs. 9.67±1.03, *P*=0.346)and total Gonadotropin dose(1427.75±210.6 vs. 1455.94±243.44, *P*=0.381). GnRH antagonist treatment duration in fixed protocol was statistically longer than the flexible protocol (6.57±1.17 vs 6.04±1.03, *P*=0.001). There was no premature LH surge in either protocol.

Conclusion(s): Fixed GnRH antagonist administration on day 5 of stimulation appear to achieve a comparable oocyte retrieved compared with flexible antagonist administration.

Trial registration: NCT02635607 posted on December 16, 2015 in clinicaltrials.gov.

Background

Gonadotrophin-releasing hormone (GnRH) antagonists have bene widely used for prevention of premature LH surges during controlled ovarian stimulation (COS) before IVF-ET. Recently two pieces of meta-analyses have indicated that GnRH antagonist protocol has a similar live-birth rate and significantly improves treatment safety as compared with long GnRH agonist protocols especially for patients with high OHSS risk[][]. Currently, there are two GnRH antagonist protocols (fixed and flexible protocol) with different timing of antagonist initiation in clinical application. To a certain extent, the fixed protocol is obviously patient-friendly, and the flexible protocol can decrease the medicine dose and treatment duration for patients[].

In a meta-analysis of four randomized controlled trials (RCTs), the fixed and flexible GnRH antagonist protocols have been found comparable in terms of the number of oocytes retrieved and clinical pregnancy rates, mainly for ovulate women with normal ovarian reserve [3][][][][]. But only one RCT including 100 infertile women with polycystic ovarian syndrome (PCOS) showed that the number of good quality oocytes and embryos in the flexible protocol were more than that in the fixed protocol with similar

antagonist dose and less FSH dose, so the flexible protocol was prone to be recommended for PCOS patients.

Generally, PCOS is regarded as the specific type of infertility patients with high OHSS risk. Due to various sensitivity of small antral follicles to exogenous FSH, flexible initiation of GnRH antagonist may be more beneficial for women with PCOS. However, no previous study directly compares the two protocols for those patients who are predicted as high ovarian responders without PCOS. Our aim was to assess the effectiveness and efficiency of the fixed versus flexible GnRH antagonist protocol in IVF/ICSI for the group patients.

Methods

Patient Population

A non-blind randomized controlled trial conducted at the Genetic and Reproductive Institution of Chongqing, China, from January 2016 to July 2017. The study was approved by our Institutional Review Board and registered on the Clinical Trial web site (ClinicalTrials.gov identifier: NCT #02635607).

Inclusion criteria were women age less than 35 years old, body mass index between 18 and 25 kg/m^2, a normal menstrual cycle with a range of 21–35 days and at least one of condition was met; 1), the number of oocyte retrieved in previous cycle was more than 15; 2), AMH ≥ 3.52 ng/ml; 3), Antral Follicle Count ≥ 16. Exclusion criteria were polycystic ovarian syndrome (Rotterdam criteria), a history of low response to FSH treatment, a history of ovariectomy, more than two previous IVF/ICSI, uterine abnormalities which included submucous fibroids, intramural fibroids larger than 3 cm in diameter, uterine malformation, intrauterine adhesions with or without history of previous surgery, more than three previous abortion, and other endocrine disorders.

204 infertile women were enrolled into the study only once after the Informed consent form was signed. The recruited women were allocated randomly into two groups. Randomization was performed using sealed opaque envelopes prepared by a third party. Randomization were done when Gn was started on menstrual cycle days 3.

Ovarian Stimulation and ART Procedures

On the day 3 of menstruation cycle, participants received a fixed dose of 150 IU of recombinant (r)FSH (Follitropin beta, Puregon, MSD) for 4 days and individually adjusted thereafter. In group A (the fixed regimen), women received daily 0.25 mg GnRH antagonist (Orgalutran, MSD) from simulation day 5 to the day of HCG administration. Women in Group B (the flexible regimen) received daily 0.25 mg GnRH antagonist (Orgalutran, MSD) on the day that the diameter of dominant follicle reached 12 mm or estradiol levels≥600 pg/ml or LH levels≥10 IU/L.

When at least three follicles were measured ≥ 17 mm in diameter, patients received their last GnRH antagonist injection in the morning and final follicular maturation was induced the same evening by 250ug rhCG (Ovidrel, Serono). If there were more than 19 follicles which were ≥ 11 mm in diameter on the day of HCG administration, final follicular maturation was induced the same evening by 0.2 mg GnRH agonist (Diphereline, Ipsen / Decapeptyl, Ferring). Oocyte retrieval took place 36–38 h after trigger by transvaginal ultrasound-guided double lumen needle aspiration. ICSI will be performed only in cases with severe male factor or previous fertilization failure. All embryo transfer will be performed after 72 h after oocyte retrieval by ultrasound guidance. One or two Day3 embryos will be transferred, and other remaining embryos will be vitrified for frozen-thawed embryo transfer cycle. All embryo cryopreservation will be performed with either circumstance as follow: (i) existed OHSS or high risk evaluated by investigator, (ii) serum P□1.5 ng/ml, (iii) hydrohystera, (iv) agonist trigger. At the following spontaneous menstrual cycle, one or two frozen embryos were thawed every time and transferred 3 days after ovulation until all embryos were transferred.

An artificial cycle was used for endometrial preparation in the next menstrual cycle. Estradiol valerate (Progynova, Delpharm Lille) at a dose of 4 to 8 mg per day was begun on day 2 or day 3 of the menstrual cycle. When the endometrial thickness reached at least 7 mm, vaginal progesterone gel at a dose of 90 mg per day (Crinone 8% gel, Serono) was added. Up to two day 3 frozen embryos were thawed and transferred 3 days after the start of progesterone. All patients will receive luteal support with 90 mg/day progesterone administered intravaginally (Crinone 8% gel, Serono) starting at the day of oocyte retrieval and continue for at least 12 weeks. Pregnancy test will be performed for at least 14 days onwards after embryo transfer.

Hormonal Assessments and Ultrasound monitoring

Hormonal assessment and ultrasound monitoring were performed on the day of menstrual cycle day 2, stimulation day 3(flexible), at initiation of the antagonist in both groups, the day after antagonist start and the day of hCG trigger and 2 weeks after embryo transfer, and additional monitoring will be decided by investigator as ovarian stimulation response. All blood samples were drawn in the morning before antagonist injection. Serum LH, FSH, hCG, E2, and P were assessed by local laboratory at the site. Ultrasound will be performed by skilled ultrasonic technician to measure and count visible follicles by the hospital’s standard procedures for the confirmation of final oocyte maturation triggered as soon as three follicles measuring ≥ 17 mm has been reached. The total numbers of follicles ≥ 11 mm need to be visibly counted.

Outcome Measures

The primary endpoint was to assess a difference in the total number of retrieved oocytes between the two groups. The secondary endpoints were the number of days and total dose of Gn and GnRH antagonist, the occurrence of premature LH surges and severe OHSS, implantation rate, clinical pregnancy rate, ongoing pregnancy rate and cumulative live birth rate (CLBR). Biochemical pregnancy was defined by serum β-hCG positive 14 days after embryo transfer. Clinical pregnancy was diagnosed by ultrasound

detection of gestational sac 2 weeks after positive hCG test. Ongoing pregnancy was defined as a pregnancy with cardiac activity proceeding beyond 12 weeks of gestation. Live birth was defined as delivery of at least one living child at 28 weeks gestation or later with heart beat and breath. All follow-up period is 3 years. The CLBRs were calculated by including the first live birth generated during the complete first IVF cycle as the numerator and all women allocated to treatment as the denominator. The estimates of the CLBR assumed that women who did not return for treatment would not have a live birth.

Statistical Analysis

Sample size calculation A sample size of 200 (1:1 allocation) achieves 80% power to detect non-inferiority of the Day-5 fixed-dose regimen as compared with the flexible protocol by a margin at -3 oocytes retrieved (3 oocytes fewer than the controlled group), using a one-sided, two-sample t-test with Mann-Whitney test adjustment at the significance level at 0.025. The true difference between the means is assumed to be 0.0 and the standard deviation of both intervention arms to be 6.8. The pre-mature discontinuation rate is set at approximately 15% for this study.

Statistical methods For the primary endpoint, mean and standard deviation (SD) on the number of oocytes will be presented. The between-group difference and corresponding 95% confidence interval (CI) (Day-5 fixed protocol – flexible protocol) will be calculated by using a two-sample t-test under the assumption that the sample data are normally distributed. A test for normality will be performed prior to the analysis on primary endpoint and possible nonparametric adjustment will be made for skewed data in terms of primary analyses. The non-inferiority will be established if the lower bound of the 95%CI in the treatment difference between two groups (Day-5 fixed protocol – flexible protocol) does not exceed − 3.0. The superiority may be claimed for the Day-5 fixed protocol if the lower bound of 95%CI for the treatment difference is above 0.0. For the secondary endpoints on categorical variables, the number and percentage of the event will be calculated and displayed. Clinical and ongoing pregnancy rates will be separately calculated and presented. Between-group comparisons will be made by Chi-square test and the corresponding 95%CI will be presented by using Miettinen-Nurminen method if the number of the observed events is at least 4. Mean and SD will be summarized for continuous variables in terms of secondary outcome measures. A treatment difference between study groups will be made by using two-sample t-test or nonparametric test whenever appropriate.

Results

A total of 204 patients participated in the study and were randomized to each two treatment groups. 3 patients were discontinued prior to oocyte aspiration due to personal reasons. 100 patients in fixed protocol group and 101 patients in the flexible protocol group were adhere to the ovarian stimulation protocol and complete the oocyte aspiration. 46 in fixed group and 47 in flexible group received fresh embryo transfer (Fig. 1). Finally, 91 patients both in fixed group and flexible group completed all embryo transfer.

The baseline population characteristics of two groups are summarized in Table 1. There were no significant differences between two groups in terms of age, body mass index (BMI), duration of infertility, and type and cause of infertility as well as ultrasonic scanning findings and hormone profiles ($p > 0.05$).

Table 1
Baseline characteristics of population

	Fixed group (n = 100)	**Flexible group (n = 101)**	***p***
Mean age(year)	28.91 ± 2.90	28.68 ± 3.31	0.601
Duration of infertility (year)	4.79 ± 2.73	4.68 ± 4.18	0.826
Body mass index(kg/m^2)	21.05 ± 1.74	21.31 ± 1.92	0.316
type of infertility			
Secondary (%)	57	48	0.205
Primary (%)	43	53	
Cause of infertility (%)			
Tubal factor	66	70	0.653
ovulation dysfunction	1	0	
Endometriosis	0	6	
Male factor	10	11	
Unexplained	11	3	
muti-factor	12	11	
AFC	10.33 ± 2.79	9.89 ± 2.73	0.260
AMH (ng/ml)	6.39 ± 2.58	5.78 ± 2.07	0.066
Baseline sex hormone			
FSH (IU/L)	5.10 ± 1.14	4.85 ± 1.27	0.144
LH (IU/L)	3.52 ± 1.34	3.32 ± 1.20	0.266
E2 (pg/ml)	29.45 ± 10.77	27.54 ± 9.76	0.189
P (ng/ml)	0.35 ± 0.14	0.34 ± 0.13	0.600

Results of the end-point analyses are presented in Table 2. The mean (SD) number of oocytes retrieved in the fixed group was 16.72(7.25) which was similar with the mean of 17.47(5.88) in the flexible group($P = 0.421$). No significant differences were observed between the two groups on Gn dose, duration of Gn

treatment and no premature LH surges was occurred. Treatment duration of GnRH antagonist in fixed protocol group was significantly longer than in flexible group(6.57 ± 1.17 vs. 6.04 ± 1.03, P = 0.001).

Table 2
Outcomes of ovarian stimulation and embryo culture and transfer

	Fixed group (n = 100)	**Flexible group (n = 101)**	**P**
Duration of rFSH (days)	9.53 ± 1.07	9.67 ± 1.03	0.346
Total amount of rFSH (IU)	1427.75 ± 210.6	1455.94 ± 243.44	0.381
Duration of GnRH antagonist (days)	6.57 ± 1.17	6.04 ± 1.03	0.001
Premature LH rise (LH > 10 IU/L)	1	2	
On Antagonist start day			
E2 (pg/ml)	629.1 ± 293.99	787.7 ± 259.48	< .0001
LH (IU/L)	2.425 ± 2.8475	2.684 ± 2.0235	0.4611
leading follicle ≥ 12 mm	22(22/100)	48(48/99)	< .0001
On hCG trigger day			
E2 (pg/ml)	3373.6 ± 1324.42	3741.0 ± 1099.39	0.034
P (ng/ml)	0.937 ± 0.4079	0.970 ± 0.4301	0.5798
No. of oocytes retrieved	16.72 ± 7.25	17.47 ± 5.88	0.421
No. of MII oocytes	14.85 ± 6.65	15.33 ± 5.49	0.577
No. of good-quality embryos	5.46 ± 3.36	5.66 ± 3.36	0.674

Table 3 show that implantation rate, clinical pregnancy rate, ongoing pregnancy rate in fresh embryo transfer and cumulative live birth rate per patients were comparable in two groups. 9 patients in flexible group developed the moderate and severe OHSS and 7 was observed in fixed group.

Table 3
c clinical outcome of embryo transfer and OHSS

	Fixed group (n = 100)	Flexible group (n = 101)	P
Fresh embryo transfer			
No. of embryo transferred	1.98 ± 0.15	2.0 ± 0	0.182
Em thickness on the day of ET	9.80 ± 1.39	10.09 ± 1.31	0.130
Implantation rate	30/91	30/94	0.8785
Biochemical pregnancy rate	27/46	29/47	0.834
Clinical pregnancy rate	24/46	24/47	0.9147
Onging pregnancy rate	20/46	17/47	0.592
Cumulative live birth rate per patients	68/100	69/101	
OHSS			
mild	35 (35.0%)	38 (37.6%)	0.6463
moderate	5 (5.0%)	4 (4.0%)	
Severe	2 (2.0%)	5 (5.0%)	

Discussion

This was the first randomized control trial to compare the clinical outcome of the fixed GnRH antagonist protocol with the flexible protocol in IVF/ICSI for the patients with predicted high ovary response except PCOS, we found no difference in total number of oocytes retrieved in the fixed protocol compared with the flexible protocol. Except the treatment duration of GnRH antagonist in the flexible protocol group was shorter than that in the fixed protocol group, no significant difference was between the two groups in term of the treatment duration and total dose of rFSH, premature LH surges, implantation, clinical pregnancy, ongoing pregnancy and cumulative live birth rate.

Previous published studies generally focused on ovulatory women and PCOS women arrived at the different outcomes. The early meta-analysis for the patients with normal ovarian response showed us that pregnancy outcome and LH surge suppression were similar between two protocols and the total treatment dose of Gn and GnRH antagonist in the flexible protocol group was less [3]. The original purpose to explore the flexible addition was to delay the initiation timing of GnRH antagonist, the flexible protocol would reduce the injection naturally but ask for more times of monitoring []. Distinctly, our study for women with predicted high ovarian response except PCOS reached the analogous results as for

normal ovary responders, which may be ascribed to similar follicular development trajectory during ovarian stimulation for the two types of patients.

However, the only 1 RCT for PCOS women revealed the diverse results that the total number of oocyte retrieval and good-quality embryo in the flexible group were remarkably more than those in the fixed group [8]. As the special type of high ovarian responders, the sensibility of follicles to FSH in PCOS patients usually was considered as lower than normal ovarian responder and other high ovarian responders []. Given the uncertain follicle development, slow ovarian response or hyperstimulation would easily occur during ovarian stimulation either due to inappropriate ovarian stimulation by exogenous FSH. So that the flexible protocol seems to be beneficial for PCOS women in clinical outcome, which is also recommended for PCOS women and poor ovarian responders by the clinical consensus on GnRH antagonist protocol in China [].

Furthermore, the possible reason why there was no significantly difference in clinical outcome between two protocols of our study is that the initiation timing of GnRH antagonist was also similar. As we known, the fixed protocol is commenced on Gn stimulation day 5 or 6, regardless of follicular development. However, the flexible protocol is administrated only when adequate follicular development (follicular size 12–14 mm) and/or E2 production by the developing follicles may give rise to premature LH surge []. Anyway, both of standards are not completely evidence based. In the flexible group of our study, according to the pre-determined initiation standards, the actual initiation timing of GnRH antagonist especially after the same dose of rFSH start was very close to fixed initiation on stimulation day 5, which both appeared to be a little earlier than other published study.

Despite the initiation timing of GnRH antagonist in the flexible group was slightly later and accordingly there were more follicles with diameter of more than 12 mm and higher serum estradiol level on antagonist initiation day, few premature LH rise was observed in two groups, rather than the premature LH surge that we concerned mostly to result the failure of ovarian stimulation. Apparently, later initiation of GnRH antagonist in the flexible protocol didn't cause a bad influence on the clinical outcome[].So far there is actually not a uniform addition standard of GnRH antagonist in flexible protocol, the GnRH antagonist initiation is mainly relied on the doctor's experience, consequently the times of monitoring and test might be increased in the clinical practice.

Meanwhile, we should realize that the number of available oocytes in ovarian stimulation depends on ovarian reserve and sufficient stimulation by exogenous FSH. For the predicted high ovarian responders except PCOS, the suitable ovarian stimulation including the dose of FSH starting and dose adjustment obviously seems to be more important in the follicle recruitment. Base on the theory of FSH threshold window, unexpected poor ovarian stimulation might be mostly attributed to insufficient FSH stimulation, GnRH antagonist is administrated too earlier with sufficient stimulation as well [16]. Then the flexible initiation of GnRH antagonist by ultrasound monitoring and serum hormone test has its advantages to avoid the predicament. Undeniably, the fixed protocol have an advantage over the flexible protocol in the aspect of reducing the treatment burden for both patients and doctors.

Certainly, our study has some limitations. First, there is no generally accepted definition of high ovarian responder, which may cause patients heterogeneity especially when sample size is not big enough. Second, RCTs per se frequently have methodological weaknesses, limiting their usefulness in clinical practice. For instance, fixed FSH starting dose may not be sufficient for all the patients, that may reduce the number of oocytes retrieved and influence the outcomes for specific patients. In addition, cumulative pregnancy rate/live birth rate including the frozen–thawed cycles might be more appropriate as key endpoint, of course that should be proven with a larger sample size. we also noted that, for the fresh embryo transfer cycles, the clinical/ongoing pregnancy rate in fixed protocol was a little numerically higher than in flexible protocol and nearly 50% cycle achieved freezing-all embryo in our study due to high risk of OHSS.

Conclusions

In conclusion, both fixed and flexible GnRH antagonist protocols can be used in controlled ovarian stimulation for IVF/ICSI for Chinese women with predicted high ovarian response except PCOS. in contrast to the flexible protocol with the same dose of 150 IU rFSH starting, the fixed protocol was patients-friendly and convenient with competitive effectiveness and efficiency.

Abbreviations

GnRH
Gonadotrophin-releasing hormone
IVF-ET
in vitro fertilization and embryo transfer
COS
controlled ovarian stimulation
OHSS
ovarian hyper-stimulation syndrome
RCT
randomized controlled trial
PCOS
polycystic ovarian syndrome
FSH
follicle-stimulating hormone
rFSH
recombinant follicle-stimulating hormone
ICSI
intra-cytoplasmic sperm injection
HCG
human chorionic gonadotrpin

rhCG
recombinant human chorionic gonadotrpin
LH
luteinizing hormone
Gn
gonadotropin
CLBR
cumulative live birth rate
BMI
body mass index

Declarations

Ethics approval and consent to participate

The experimental protocol was established according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Chongqing health center for women and children. Written informed consent was obtained from individual participants.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

The present work was designed by HY. The third party generated the random allocation sequence, XL and FL enrolled participants. XL, FL and LP were assigned participants to interventions. Data extraction and analysis were performed by XL . XL and CL participated in the data collection. GH and HY participated in revisions to the article. All authors have read and approved the final manuscript.

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Figures

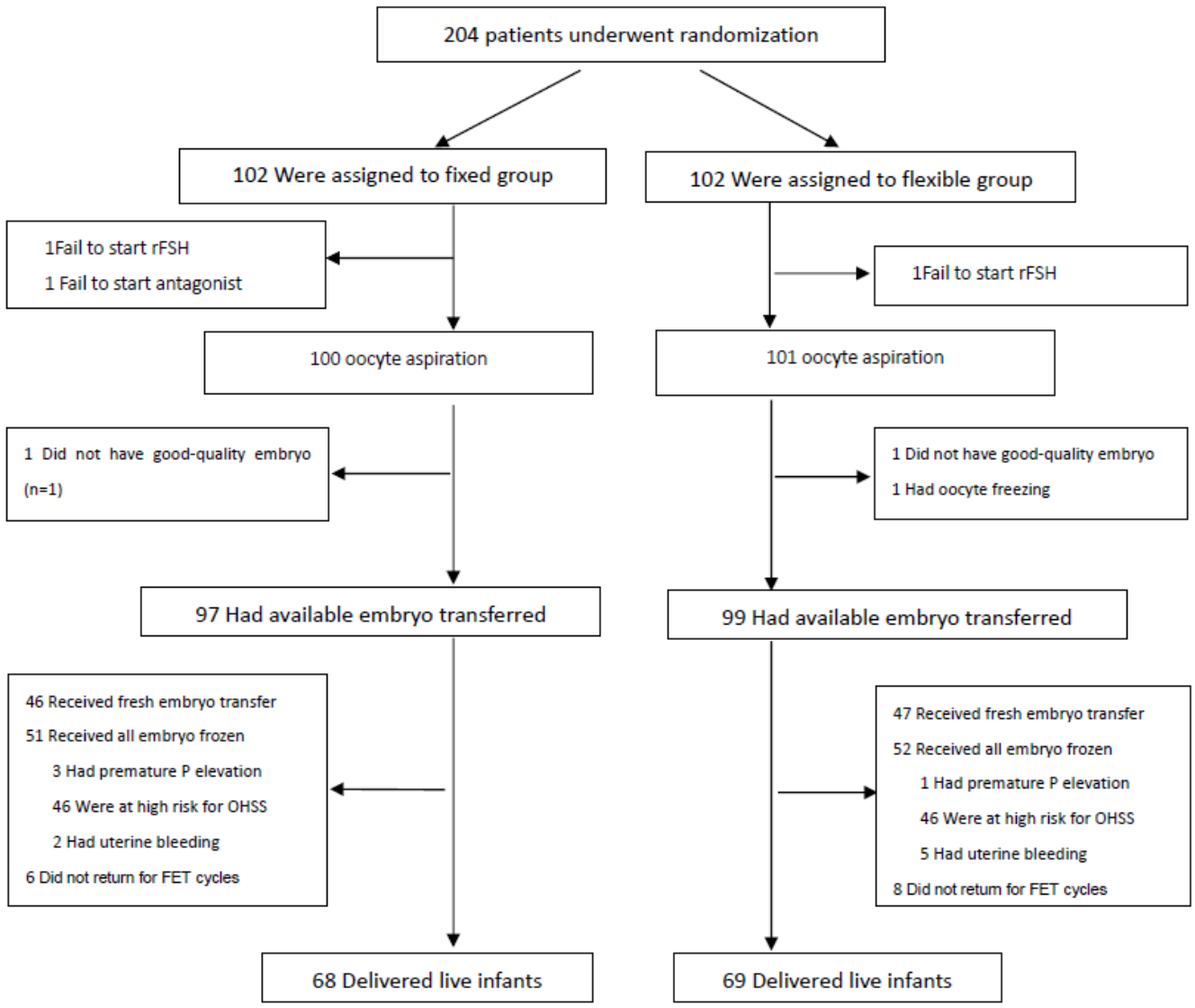

Figure 1

Flow chart on subject disposition.

Supplementary Files

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- CONSORTChecklist.doc
- CONSORTFlowDiagram.pdf