Cumulative Live Birth Rates in Patients with Polycystic Ovary Syndrome: Comparing Progestin Primed Ovarian Stimulation Protocol and GnRH-Antagonist Protocol

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Research

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Abstract

Background: Cumulative live birth rate (CLBR) becomes a comprehensive and meaningful indictor of the success of IVF nowadays. Frozen-embryo transfer (FET) was associated with a higher rate of live birth and a lower risk of the ovarian hyperstimulation syndrome (OHSS) in polycystic ovary syndrome (PCOS) patients. Progestin-primed ovarian stimulation (PPOS) is a new ovarian stimulation protocol in which oral progestin been used to prevent premature luteinizing hormone (LH) surges during ovarian stimulation. The purpose of the current study is to investigate the CLBR of an in vitro fertilization (IVF) cycle in women with PCOS following PPOS protocol compared with gonadotropin releasing hormone (GnRH) antagonist protocol.

Methods: It is a retrospective study. The first IVF cycle of 666 PCOS women were included. Ovarian stimulations were performed with PPOS or GnRH antagonist protocol. All patients included in the analysis had either delivered a baby or had used all their embryos of their first stimulated cycle. The patients were followed for 2–7 years until February 2020.

Result(s): The CLBR were similar in the PPOS and GnRH antagonist group (64% vs 60.1%, P = 0.748). Logistic regression analyses showed treatment protocol (PPOS vs GnRH antagonist) did not show any significant correlation with the CLBR (adjusted OR: 0.898; 95% CI: 0.583-1.384, P=0.627). No statistically significant differences were found in the live birth rates per embryo transfer (41.3% vs. 38.4%) in the study group and controls.

Conclusion(s): The results of this study showed that both the live birth rate per embryo transfer and the cumulative live birth rate were similar between PPOS and GnRH antagonist group. PPOS protocol is efficient in the controlled ovarian stimulation of patients with PCOS.

Background

Polycystic ovary syndrome (PCOS) is the most popular endocrine disorder which affects 9–21% reproductive age women [1–3]. It accounts for about 80% of women with anovulatory infertility [4].In vitro fertilization (IVF) is a commonly used infertility treatment for PCOS patients who fail to conceive with ovulation induction or if there are concomitant infertility factors such as tubal damage or male subfertility. However, there are many concerns about the efficacy and safety of this procedure. Women with PCOS who require IVF are at high risk of ovarian hyperstimulation syndrome (OHSS), a potentially life-threatening complication [5, 6].Moreover, after achieve pregnancy through IVF, PCOS women are associated with increased risk of maternal and neonatal complications, including gestational diabetes mellitus, pregnancy-induced hypertension, preterm birth, large-for-gestational-age babies, etc[7–11].Careful strategies are needed to minimize these risks.

Several recent multicenter randomized controlled trial have demonstrated that the “freeze-all” strategy (all the embryos transferable were cryopreserved for later transfer) is not only associated with a higher live birth rate(LBR) but also a lower risk of the OHSS and pregnancy complications in PCOS patients treated

for IVF [12, 13]. For this reason as well as the progress of vitrification, protocols used for controlled ovarian stimulation (COS) in PCOS women need not consider whether or not fresh ET can be applied.

GnRH antagonist protocol is now the most commonly used COS protocol in PCOS patients due to the significantly reduced risk of OHSS especially when gonadotropin releasing hormone agonist (GnRHa) was used for trigger [14–16]. However, GnRH antagonist is expensive. Progestin-primed ovarian stimulation (PPOS) is a new stimulation protocol in which oral progestin been used as an alternative to GnRH analog to prevent premature LH surges during ovarian stimulation. In this protocol, ovulation was co-triggered with GnRH agonist and low dose hCG and “freeze-all” strategy was applied. It has been reported that this protocol yields a similar or even better pregnancy outcome per embryo transfer cycle compared with conventional gonadotropin releasing hormone agonist (GnRHa) short protocol [17–19]. In addition, oral progestin has the advantage of being convenient and cheap.

Traditionally, the success of IVF has been reported as live birth rates of fresh embryo transfer. Cumulative live birth rate (CLBR) is defined as the rate of deliveries resulting from the transfer of all (fresh plus frozen-thawed) embryos from the same stimulation. Nowadays, with the improvements of vitrification, CLBR becomes a comprehensive, relevant and meaningful indictor of the success of IVF [20–22].

The literatures on the use of PPOS protocol in women with PCOS for IVF only investigating the clinical pregnancy rate or ongoing pregnancy rate per transfer, cumulative success rate especially CLBR had not been showed in those studies [18]. Furthermore, their study compared PPOS protocol with GnRH agonist short protocol, which is rarely used in COS of PCOS patients nowadays.

The aim of the present study was to evaluate the effectiveness of PPOS protocol in PCOS women referred for their first ART cycle through comparing the cumulative live birth rate of it with GnRH antagonist protocol.

Materials And Methods

Study design

This was a retrospective analysis including PCOS women who performed their first artificial reproductive technology (ART) cycle with PPOS protocol or GnRH-antagonist protocol in our centre from July 2013 to June 2018. The cycles were followed to February 2020.The objective of this study was to compare cumulative live birth rate of PPOS protocol and GnRH-antagonist protocol. The study was approved by the institutional ethics committee of The First Affiliated Hospital of USTC.

Participants

PCOS was diagnosed according to Rotterdam consensus as fulfilling at least two of the three criteria: 1) oligo-anovulation or anovulation;2) clinical or biochemical signs of hyperandrogenism; and 3)polycystic ovarian morphology on ultrasound, as defined by at least one ovary with ≥12 follicles or volume ≥ 10 cm^3[23]. Exclusion criteria were: other causes of hyperandrogenism and ovulation dysfunction; patients

20 or >40 years of age at oocyte retrieval; history of recurrent miscarriage; congenital uterine malformations; abnormal chromosome karyotype, preimplantation genetic diagnosis (PGD) cycles, no embryo transferable cycles.

Treatment protocols

GnRH antagonist protocol

Recombinant FSH (Gonal-f; Merck Serono, Geneva, Switzerland) was started on Days 2–3 of the progesterone induced or spontaneous menstrual cycle and continued until the day of ovulation induction. The initiation doses will be 112.5 IU/day for patients weighing ≤60 kg and 150 IU/day for patients weighing >60 kg. At day 5-6 of ovarian stimulation, the rFSH doses were adjusted according to ovarian response evaluated by transvaginal ultrasonography and serum hormone tests. GnRH antagonist (Cetrorelix; Merck Serono, Darmstadt, Germany) at a daily dose of 250μg was started when the largest follicle exceeded 12 mm. Recombine human chorionic gonadotropin (r-hCG) 250ug (Ovitrelle; Merck Serono, Geneva, Switzerland) was administered to trigger oocyte maturation when two or more follicles were ≥18 mm. If the patients were at highly risk of ovarian hyperstimulation syndrome (OHSS) (over 16-18 follicles were >11 mm diameter on the day of triggering), ovulation triggering was performed either by administration of triptorelin 0.2 mg (Decapeptyl, Ferring Pharmaceuticals, Netherlands) or by triptorelin 0.2 concomitant with 1000 IU of hCG. In that case, “freeze-all” strategy was applied.

PPOS protocol

Ovarian stimulation was initiated on menstrual cycle Day 2-3 with daily injection of r-FSH (Gonal-f; Merck Serono, Geneva, Switzerland) combined with oral MPA (6-8 mg/d, Shanghai Xinyi Pharmaceutical Co., China). The initiation doses was 112.5 IU/day for patients weighing ≤60 kg and 150 IU/day for patients weighing >60 kg also. After 5 days of stimulation, transvaginal ultrasound scans and serum hormone tests will be performed to adjust FSH doses. When three dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was co-triggered by triptorelin 0.2 mg (Decapeptyl, Ferring Pharmaceuticals, Netherlands) and hCG 1000 IU (Lizhu Pharmaceutical Trading Co., China).

Transvaginal ultrasound–guided oocyte retrieval was performed 34–36 h after trigging. Collected oocytes were inseminated either via conventional IVF or ICSI. Embryos were examined on Day 3 after insemination. Two good-quality embryos (including grade 1 and grade 2 6-8-cell embryos) were frozen by vitrification on the third day after oocyte retrieval. Surplus embryos were placed in extended culture to day 5 or day 6. Embryos were graded as 1(good), 2(reasonable), or 3(moderate) according to the number of cells, degree of fragmentation and renewed development of the embryo. This standard was based on the ESHRE Istanbul consensus on embryo assessment [24]. Only grade 1-3 blastocysts were frozen. The laboratory procedure of vitrification and warming for Day 3 embryos was the same as the method used for human oocytes reported by Tong et al [25]. For blastocysts, a glass micro-needle was used to collapse the blastocyst before vitrification. The following steps were the same as for the Day 3 embryos.ET was

performed under ultrasound guidance. Intravaginal progesterone gel (Crinone gel 8%, Serono) was administered for luteal phase support from the day after oocyte retrieval until 8-10 weeks of pregnancy.

In order to ensure validation of complete cycles, this study only involved patients who had already used all their frozen embryos from the present oocyte retrieval or gave live birth to a child.

Fresh embryo transfer

Fresh ET was intended for the patients triggering with hcg and no signs of early OHSS in GnRH antagonist protocol. OHSS was diagnosis according to the guideline of Practice Committee of the American Society for Reproductive Medicine [26].

Frozen–thawed embryo transfer

'Freeze-all' strategies were applied in PPOS group. For patients triggering with in triptorelin or at high risk of OHSS in GnRH antagonist group, 'Freeze-all' strategies were also applied. In this study, endometrium preparation method of FET was the same in the two groups. In brief, hormone replacement treatment cycle or letrozole-induced- ovulation cycle was choose based on the discretion of physicians and/or patients' preference. In letrozole -induced- ovulation cycle, letrozole 5 mg was administered for 5 days, and then, follicle growth was monitored beginning on day 10. If no dominant follicles were found, a low dose of HMG (75 IU/day) was used to stimulate follicle growth and endometrial lining.Day-3 ET was performed 4 days after spontaneous or hCG-induced LH surge while blastocyst transfer was performed 6 days after spontaneous or hCG-induced LH surge. In hormone replacement treatment cycle, estradiol valerate (progynova, Schering, German) was taken 6 mg/d from menstrual cycle day 2-3. An ultrasound assessment was done 12 to 14 days later to assess endometrium thickness. Progesterone 40 mg/d which would be changed to 60 mg/d 2 days later, was given to transform the endometrium, provided the endometrial thickness exceeded 8 mm. Embryo transfer was performed 4 days after progesterone administration for day-3 embryos or 6 days later for blastocysts.

Main outcome measure and statistical analysis

The primary outcome was the CLBR defined as the delivery rate of a live infant (>24 weeks of gestation) in fresh or subsequent FET cycles in relation to one oocyte retrieved. Only the first delivery was considered in the analysis.

All analyses have been performed using IBM Spss statistics 21.For continuous variables, Student's t-test and Mann–Whitney test were used for data with homogeneous variance and heterogeneous variance respectively. The x^2 test was used for categorical variables. Logistic regression analyses were conducted to identify independent correlates between each possible confounding factor, especially treatment protocol and cumulative LBR after adjusting for other confounders that were identified in our univariate analysis. P<.05 was considered statistically significant.

Results

Patient characteristics

Of the total of 666 women who were assessed for eligibility, 328 cases were involved in the study group (PPOS group) and 338 to the control group (GnRH antagonist group). Baseline characteristics of the patients in this study are shown in Table I. Age, BMI, basal sex hormone (FSH, LH, E2, T) value and duration of infertility were comparable between the two groups. Also, there was no significant difference in indications for ART between the two groups. In the study, 40/328（12.2%）of the study group and 37/338 (10.9%) of the control group had previously delivery(p=0.755).

Ovarian Stimulation, Follicle Development, Oocyte Performance

Table II describes the ovarian stimulation characteristics and embryological outcomes of ovarian stimulation treatment in both groups.

The total gonadotropin（Gn）dose was comparable between PPOS group and GnRH antagonist protocol (2209.5±1372.5 versus 2170.5±1155IU, P = 0.426). There was no statistical difference in mean stimulation duration between the two groups [11.67（5-25）versus. 11.83（6-26）, P = 0.854].Also, no significantly difference was found in oocyte number between PPOS group and GnRH antagonist group [14.83 (2-50) versus. 15.08(2-46), P > 0 .05].The mean number of high-quality cleaved embryos was 6.38(0-20) in the PPOS group and 5.79(0-32) in the GnRH antagonist group (P = 0.462).

Similarly, there was no significant difference in cryopreserved day 5/6 embryos between the two groups (P > 0.05). There was only 1 patient in PPOS group experienced moderate OHSS during the study, while in GnRH antagonist group there were 12 patients suffered early OHSS and 3 patients suffered later OHSS(P＜0.000).

Embryo characteristics and reproductive outcome

Embryo characteristics and reproductive outcome are listed in Table III. The proportion of blastocysts transfer was similar between the study group and the GnRH antagonist group (42.6%vs. 37.1%, p=0.186).Also, the proportion of double embryo transfer was similar between the study group and the GnRH antagonist group (60.7%vs. 61.1%,p=0.934).The number of blastocysts transferred [1.27(1-2)vs. 1.36(1-2)]and number of day-3 embryos transferred in FET cycles [1.95(1-2)vs. 1.99(1-2)] showed no significant difference between the two groups (P>0.05).The live birth rate per transfer was 210/509 (41.3%) in the study group, while the live birth rate per transfer in the GnRH antagonist group was 203/529(38.4%).No significantly difference was found in the cumulative pregnancy rate between the two groups (210/328 (64%) vs. 203/338 (60.1%); P>0.05).

Prognostic covariate analyses

In the Logistic regression analyses model for both the PPOS and antagonist groups, age had a significant influence on the CLBR (adjusted OR: 0.918; 95% CI: 0.867-0.973; P = 0.004). BMI and duration of infertility did not show any significance in the model, adjusted OR being (0.981; 95% CI: 0.929-1.035) and (0.974; 95% CI: 0.881-1.076).

The number of retrieved oocytes, as a continuous variable, show significant correlation with the CLBR (adjusted OR: 1.037; 95% CI: 1.010-1.065). Treatment protocol (PPOS or GnRH antagonist) did not show any significant correlation with the CLBR (adjusted OR: 0.898; 95% CI: 0.583-1.384, P=0.627).

Discussion

The results of the study provided first-time evidence that, compared with GnRH antagonist protocol, PPOS protocol resulted in a similar cumulative live birth rate among patients with PCOS.PPOS protocol is effective for COS in PCOS women undergoing IVF. Our study indicated that the embryos originating from this regimen had similar developmental potential as those from the GnRH antagonist protocol. These results will help establish a new regimen for ovarian stimulation in women with PCOS.

In the study of Kuang et al, it was found that the duration and dose of gonadotropin in PPOS protocol were higher than GnRH short protocol [17]. Another study by Wang et al showed that the duration of gonadotropin administration was similar between PPOS protocol (MPA10 mg and hMG) and GnRH agonist short protocol, but gonadotropin dose was significantly higher in PPOS protocol [18].Different from their study, we found that both the duration of stimulation and the Gn dose were comparable between PPOS group and GnRH antagonist protocol. A potential explanation for this discrepancy is the fact that in this two previous study, a dose of 10 mg MPA was choose for hypothalamic-pituitary-ovarian (HPO) axis suppression during ovarian stimulation which may lead to stronger pituitary suppression [27, 28]. In our study, we decrease the MPA dose to 6–8 mg and found that 6–8 mg MPA is efficient for preventing premature LH surge in PCOS women. This dose may alleviate pituitary suppression and decrease Gn dose at the same time. Further research is needed to explore the optimal dose of MPA.

Kuang et al compared PPOS protocol with GnRH agonist short protocol and showed that the rates of oocyte retrieval, mature oocytes, fertilization, and cleaved embryos were similar between the two groups. The FET results also proved that the embryos from the PPOS protocol had similar developmental potential compared with GnRH agonist short protocol [17]. Wang et al reported the comparable pregnancy outcome of PPOS protocol compared with GnRH agonist short protocol in PCOS patients [18]. The study of Zhu et al suggested that PPOS protocol using Utrogestan to block the LH surge showed a better clinical outcome compared with GnRH agonist short protocol [19]. Our study showed that the oocyte retrieved, high-quality cleaved embryos, blastocyst formation rate and cumulative live birth rate were comparable between the PPOS group and the GnRH antagonist group. The results support that PPOS protocol is effective and feasible in COS for PCOS patients during their IVF treatment.

Previous study of high responders demonstrated that transfer of frozen-thaw embryos associated with comparable or better reproductive outcomes and low risk of OHSS than fresh embryo [13, 29–32]. These

previous studies reported only reproductive outcomes per first transfer for women in the ‘freeze-all’ group compared with those in the ‘fresh-transfer’ group. Evaluate IVF success rates based on per embryo transfer alone is incomplete and inappropriate [33]. Cumulative live birth rate per oocyte retrieval summarizes the chance of live birth during an entire treatment period [21, 33]. To date, there have been only a limited number of randomized controlled studies (RCTs) compared cumulative live birth rate of ‘freeze-all’ versus ‘fresh-transfer’ strategy [34].The result of Li et al demonstrated that the cumulative live birth rate of ‘freeze-all’ strategy is similar as the ‘fresh-transfer’ strategy among high responders [35]. None of previous study has compared the cumulative live birth rate of high responders between different treatment protocols. This is to our knowledge, the first study comparing CLBR between PPOS and GnRH antagonist protocols. We included women with PCOS referred for their first IVF cycle within the age range of 20–39 years. As PCOS is highly prevalent [2, 36] in infertility patients, these results may be benefit for a large proportion of patients seeking IVF treatment. The result of this study showed that the CLBRs were comparable between PPOS group and GnRH antagonist group, with 64% and 60.1% achieving at least one live birth respectively. The result of our study demonstrated that PPOS protocol is as effective as GnRH antagonist protocol for COS in women with PCOS.

Ovarian hyperstimulation syndrome (OHSS) is a severe iatrogenic complication of ovulation induction during assisted reproduction. Occurrence of OHSS depends upon hCG, either following hcg trigger during COS (Early OHSS) or an endogenous increase from the initiated pregnancy (Late OHSS) [37, 38].Women with PCOS have a priori risk for development of OHSS. Many efforts have been made to prevent the occurrence of OHSS. Among them, the ‘freeze-all’ strategy and GnRH agonist trigger is the two most important methods [39, 40]. Using PPOS protocol, these two methods can be combined the same as GnRH antagonist protocol [17].In our study, low dose of hCG (1000 IU) was used combined with GnRHa to triggering ovulation in PPOS group. The result demonstrated that the risk of moderate or severe OHSS was not increased (only 1 early moderate OHSS occurred).

In line with the results from the between-group analysis, the multivariable regression analysis for CLBR showed that the only significant predictors were the number of oocytes retrieved and the age, whereas BMI and treatment protocol were not significantly associated.

Cost-effectiveness is a main concern for infertility patients seeking treatment. Instead of GnRH antagonist, MPA is used for down-regulation in PPOS protocol.MPA is much cheaper than GnRH antagonist agents. As the result of our study showed that the Gn dose were comparable between PPOS and GnRH antagonist protocol, the PPOS protocol is cost-effective owing to the less costly of MPA compared to GnRH antagonist. Evans et al. assessing the cost-effectiveness of ovulation suppression with progestins compared with GnRH analogues in IVF cycles, progestins were found to be cost-effective compared with GnRH antagonist in “freeze-all” cycles [41]. The result of our study is in line with this study.

We recognize there are some limitations in our study. The retrospective nature of this analysis may be subject to selection bias regarding the type of COS protocol (PPOS vs. GnRH antagonist). In this regard,

we only involved women undergoing their first IVF/ICSI cycles and meticulously screened patients with the use of strict criteria. Moreover, the baseline characteristics of the two groups were comparable. The sample size of our study need be enlarged. Future RCTS on this subject are needed to look into the details on the effect of PPOS protocol on the COS of PCOS patients.

Conclusion

The results of this study showed that both the live birth rate per embryo transfer and the cumulative live birth rate were similar between PPOS and GnRH antagonist group. PPOS protocol is efficient in the controlled ovarian stimulation of patients with PCOS treated for IVF.

Abbreviations

CLBR：cumulative live birth rate;FET：frozen-embryo transfer; OHSS：ovarian hyperstimulation syndrome; PPOS：progestin-primed ovarian stimulation; LH：luteinizing hormone; IVF: in vitro fertilization; GnRH： gonadotropin releasing hormone; COS：controlled ovarian stimulation; GnRHa: gonadotropin releasing hormone agonist; ART：artificial reproductive technology; PGD preimplantation genetic diagnosis; rFSH recombinant follicle stimulating hormone; r-hCG：recombine human chorionic gonadotropin; Gn： gonadotropin;HPO hypothalamic-pituitary-ovarian

Declarations

Ethics approval and consent to participate

The Ethics Committee of The First Affiliated Hospital of USTC approved this study protocol, and informed consent was waived from each individual.

Consent for publication

Not applicable.

Availability of data and materials

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

Conflicts of interests

None declared.

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Authors’ contributions

J.J. was involved in substantial contributions to conception and design, acquisition, analysis and interpretation of data, drafting and revising the article and final approval of the version to be published; L.H. was involved in contributions to analysis and interpretation of data and final approval of the version to be published; L.L. was involved in contributions to acquisition of data and final approval of the version to be published.

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Tables

Table I
Baseline characteristics on menstrual cycle Days 1–3 in women treated with either PPOS or GnRH antagonist.

	PPOS group(n = 328)	Antagonist group(n = 338)	P
Age at inclusion (year)	29.3(21–39)	28.64(20–39)	0.064[a]
BMI (kg/m2),	23.25(16.8–32.5)	23.47(16.41–33.87)	0.756 [a]
Duration of infertility (years),	3.36(1–16)	3.11(1–10)	0.733 [a]
Previous pregnancy, % (n)	130/328(39.69%)	126/338(37.3%)	0.677[b]
Previous delivery, n (%)	40/328(12.2%)	37/338 (10.9%)	0.755 [b]
Indication for IVF n (%)			0.372 [b]
PCOS only	80/328 (24.4%)	93/338 (27.5%)	
PCOS + male factor	62/328 (18.9%)	76/338 (22.5%)	
PCOS + tubal factor	173/328 (52.7%)	139/338 (41.0%)	
PCOS + other	13/328 (4.0%)	30/338 (8.88%)	
bFSH (IU/L)	4.48 ± 3.26	4.81 ± 3.34	0.598 [c]
bLH (IU/L)	3.84 ± 4.26	4.39 ± 4.11	0.32 [c]
bE2 (pg/mL)	31.67 ± 28.34	30.86 ± 24.52	0.859 [c]
T	0.3820 ± 0.368	0.364 ± 0.285	0.736 [c]

a Two-sample Mann–Whitney test. Values are median (minimum–maximum).b Pearson x2 test. Values are number (percentage).c Two-sample t-test. Values are mean + SD.

Table II
Treatment characteristics in women allocated to either PPOS or GnRH-antagonist protocol.

	PPOS group(n = 328)	GnRH antagonist group(n = 338)	P-value
Days of stimulation(day)	11.67(5–25)	11.83(6–26)	0.854 [a]
Total dose of Gonadotrophins(IU)	2209.5 ± 1372.5	2170.6 ± 1155	0.426 [b]
Oocyte retrieve(n)	14.83(2–50)	15.08(2–46)	0.729 [a]
Fertilized oocytes (n)	10.21(1–47)	9.82(1–38)	0.386 [a]
high-quality Cleaved embryos (n)	6.38(0–20)	5.79(0–32)	0.462 [a]
Cryopreserved day 5/6 embryos (n)	3.45(0–12)	3.04(0–16)	0.36 [a]
Early moderate/severe OHSS n/n (%)	1/328 (0.30%)	12/338 (2.67%)	0.000 [c]
Late moderate/severe OHSS n/n (%)	0	3/338 (0.89%)	0.000 [c]

a Two-sample Mann–Whitney test. Values are median (minimum–maximum) b Two-sample t-test. Values are mean + SD. c Pearson x2 test. Values are number (percentage).

Table III
Embryo characteristics and reproductive outcome in women treated either with PPOS or GnRH-antagonist protocol.

	PPOS group(n = 328)	GnRH antagonist group (n = 338)	P-value
Blastocyst transfer, n/n (%)	217/509 (42.6%)	196/529 (37.1%)	0.186 c
Day-3 embryo transfer, n/n (%)	292/509 (57.4%)	333/529(62.9%)	
number of blastocysts transferred in FET cycles	1.27(1–2)	1.36(1–2)	0.180 a
number of Day-3 embryos transferred in FET cycles	1.95(1–2)	1.99(1–2)	0.106 a
Double embryo transfer n/n (%)	309/509 (60.7%)	323/529 (61.1%)	0.934 c
Single embryo transfer n/n (%)	200/509 (39.3%)	206/529 (38.9%)	
Live birth rate per ET	210/509 (41.3%)	203/529 (38.4%)	0.508 a
Cumulative live birth, n (%)	210/328 (64%)	203/338 (60.1%)	0.748 a
a Pearson x2 test. Values are number (percentage) b Two-sample Mann–Whitney test. Values are median (minimum–maximum)			

Table
Multivariable analysis of variables for cumulative live birth rate

	Unadjusted ORs	P-value	Adjusted ORs (95% CI)	P-value
Age (year)	0.906(0.859–0.956)	0.000	0.918(0.867–0.973)	0.004[a]
Duration of infertility (year)	0.921(0.841–1.009)	0.077	0.974(0.881–1.076))	0.606[a]
No. of oocytes	1.043(1.016–1.071)	0.001	1.037(1.010–1.065)	0.007[a]
BMI	0.959(0.912–1.009)	0.104	0.981(0.929–1.035)	0.478[a]
Treatment protocol				
PPOS	0.944(0.621–1.453)	0.787	0.898(0.583–1.384)	0.627[b]
Antagonist group	Reference		Reference	

a P-value of each variable's overall effects after adjusting for the other variables. b P-value between each variable's subgroups and reference group.