Cost-Effectiveness of Antagonist Protocol versus Short-Acting Long Protocol in Fresh Embryo Transfer: A Propensity Score Matching Study (Postprint)

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Abstract

Background: In the field of assisted reproduction, patients' treatment costs are increasingly considered as an important basis for formulating treatment plans, while domestic health economics research on the application of antagonist protocols versus short-acting long protocols in fresh embryo transfer is relatively scarce. Objective: To conduct a cost-effectiveness analysis of the clinical outcomes of antagonist protocols versus short-acting long protocols in fresh embryo transfer based on propensity score matching (PSM).

Methods: A total of 1,971 patients who underwent in vitro fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) treatment at the Reproductive Medicine and Genetic Center of Guangxi Zhuang Autonomous Region People's Hospital from 2016 to 2018 were selected, comprising 2,117 treatment cycles. Based on the controlled ovarian hyperstimulation (COH) protocol, they were divided into an antagonist protocol group (422 patients, 432 cycles) and a short-acting long protocol group (1,549 patients, 1,685 cycles). Baseline patient data [including female age, infertility type, infertility duration, body mass index (BMI), menarche age, gravidity, baseline follicle-stimulating hormone (FSH), baseline estradiol (E2), baseline luteinizing hormone (LH), baseline progesterone, antral follicle count (AFC), etc.], treatment indicators [including COH protocol, gonadotropin (Gn) usage days, total Gn dosage, trigger day E2, trigger day LH, trigger day progesterone, trigger day endometrial thickness, number of oocytes retrieved, number of mature oocytes, fertilization method, number of transferable embryos, number of high-quality embryos, number of transferred embryos, etc.], and clinical outcomes (including non-pregnancy, miscarriage, ectopic pregnancy, and live birth) were collected from the electronic medical record system. R 4.1.1

software was used for 1:1 propensity score matching with a caliper value set at 0.2. Cost-effectiveness analysis was performed on the matched two groups, and sensitivity analysis was applied to verify the robustness of the study conclusions.

Results: Before PSM, there were statistically significant differences between the two groups in female age, BMI, baseline FSH, baseline LH, and AFC (P<0.05). After PSM, each group had 390 cycles, with no statistically significant differences in female age, BMI, baseline FSH, baseline LH, and AFC between the two groups (P>0.05). Treatment indicators: After PSM, the antagonist protocol group had lower Gn days, total Gn dosage, trigger day E2, trigger day endometrial thickness, number of oocytes retrieved, and number of mature oocytes, but higher trigger day LH compared with the short-acting long protocol group (P<0.05). Clinical outcomes: After PSM, the antagonist protocol group had lower clinical pregnancy rate (43.08% vs 54.62%, P=0.001), implantation rate (29.15% vs 37.01%, P=0.001), and live birth rate (33.59% vs 44.10%, P=0.003) than the short-acting long protocol group. After PSM, the median per-cycle ovulation induction drug cost and median per-cycle total cost in the antagonist protocol group were lower than those in the short-acting long protocol group (P<0.05). Using live birth rate as the endpoint indicator of this study, cost-effectiveness analysis showed that the cost per live birth achieved was 66,397.92 yuan in the antagonist protocol group and 54,226.33 yuan in the short-acting long protocol group, with an incremental cost-effectiveness ratio of 15,325.88 yuan, which is less than the 2018 Chinese per capita GDP (64,644 yuan). Sensitivity analysis results were basically consistent with the base-case analysis results.

Conclusion: In fresh embryo transfer cycles, treatment using the short-acting long protocol is superior to the antagonist protocol in both clinical outcomes and cost-effectiveness.

Full Text

Cost-Effectiveness Analysis of GnRH Antagonist Protocol and Short-Acting GnRH Agonist Long Protocol in Fresh Embryo Transfer Based on Propensity Score Matching

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Abstract

Background: In the field of assisted reproductive technology, patient treatment costs are increasingly considered a critical factor in clinical decision-making. However, domestic health economics research comparing the cost-effectiveness of gonadotropin-releasing hormone (GnRH) antagonist protocols versus short-acting GnRH agonist long protocols in fresh embryo transfer remains limited.

Objective: To conduct a cost-effectiveness analysis of clinical outcomes between GnRH antagonist and short-acting GnRH agonist long protocols in fresh embryo transfer cycles using propensity score matching (PSM).

Methods: We retrospectively analyzed 1,971 patients who underwent 2,117 cycles of in vitro fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) at the Reproductive Medicine and Genetics Center of People's Hospital of Guangxi Zhuang Autonomous Region between 2016 and 2018. Patients were divided into an antagonist protocol group (422 patients, 432 cycles) and a short-acting long protocol group (1,549 patients, 1,685 cycles) based on their controlled ovarian hyperstimulation (COH) regimen. Baseline data [including female age, infertility type/duration, body mass index (BMI), menarche age, gravidity, baseline follicle-stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), progesterone, and antral follicle count (AFC)], treatment indicators [including COH protocol, gonadotropin (Gn) duration and dosage, trigger-day E2/LH/progesterone, endometrial thickness, oocyte retrieval numbers, mature oocyte numbers, fertilization method, transferable embryo count, high-quality embryo count, and number of embryos transferred], and clinical outcomes (non-pregnancy, miscarriage, ectopic pregnancy, and live birth) were extracted from electronic medical records. PSM was performed using R 4.1.1 software with 1:1 nearest-neighbor matching and a caliper value of 0.2. Cost-effectiveness analysis was conducted on the matched cohorts, and sensitivity analyses were performed to verify robustness.

Results: Before PSM, significant differences existed between groups in female age, BMI, baseline FSH, baseline LH, and AFC ($P<0.05$). After PSM, 390 cycles were included in each group, with no significant differences in baseline characteristics ($P>0.05$). Treatment indicators after PSM showed that the antagonist protocol group had significantly lower Gn duration, total Gn dosage, trigger-day E2, endometrial thickness, retrieved oocyte count, and mature oocyte count, but higher trigger-day LH compared to the short-acting long protocol group ($P<0.05$). Clinical outcomes after PSM revealed that the antagonist protocol group had significantly lower clinical pregnancy rate (43.08% vs. 54.62%, $P=0.001$), implantation rate (29.15% vs. 37.01%, $P=0.001$), and live birth rate (33.59% vs. 44.10%, $P=0.003$) than the short-acting long protocol group. The median per-cycle ovulation induction drug cost and total cost were also significantly lower in the antagonist protocol group ($P<0.05$). Using live birth rate as the primary endpoint, the cost per live birth was ¥66,397.92 in the antag-

onist protocol group and ¥54,226.33 in the short-acting long protocol group, yielding an incremental cost-effectiveness ratio (ICER) of ¥15,325.88—well below the willingness-to-pay threshold of one times China's 2018 per capita GDP (¥64,644). Sensitivity analyses confirmed the robustness of these findings.

Conclusion: In fresh embryo transfer cycles, the short-acting GnRH agonist long protocol demonstrates superior clinical outcomes and economic performance compared to the GnRH antagonist protocol.

Keywords: Infertility, female; Embryo transfer; Ovulation induction; Clinical pregnancy; Live birth rate; Cost-effectiveness analysis; Propensity score matching

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1. Methods

1.1 Study Population

We selected patients who underwent IVF/ICSI-ET treatment at the Reproductive Medicine and Genetics Center of People's Hospital of Guangxi Zhuang Autonomous Region between 2016 and 2018. Inclusion criteria were: (1) compliance with ethical principles of assisted reproductive technology; (2) both partners meeting IVF/ICSI-ET indications with no contraindications; (3) use of either antagonist protocol or short-acting long protocol; (4) fresh embryo transfer cycles; and (5) complete follow-up records. Exclusion criteria included: (1) sexually transmitted diseases, acute urogenital infections, or severe psychiatric disorders in either partner; (2) genetic diseases deemed unsuitable for reproduction per the Maternal and Infant Health Care Law that could not be addressed by preimplantation genetic diagnosis; (3) drug abuse or severe harmful habits; (4) exposure to teratogenic substances, medications, or radiation during the active period; and (5) uterine inability to sustain pregnancy. A total of 1,971 patients undergoing 2,117 treatment cycles met the inclusion criteria, comprising 422 patients (432 cycles) in the antagonist protocol group and 1,549 patients (1,685 cycles) in the short-acting long protocol group. All patients provided informed consent, and the study was approved by the Ethics Committee of People's Hospital of Guangxi Zhuang Autonomous Region (Approval No.: KY-ZC-2021-129).

1.2 Data Collection

We extracted the following data from electronic medical records: (1) Baseline characteristics including female age, infertility type/duration, BMI, menarche age, gravidity, baseline FSH, E2, LH, progesterone, and AFC; (2) Treatment indicators including COH protocol, Gn duration and dosage, trigger-day E2/LH/progesterone, endometrial thickness, retrieved oocyte count, mature oocyte count, fertilization method, transferable embryo count, high-quality em-

bryo count, and number of embryos transferred; and (3) Clinical outcomes including non-pregnancy, miscarriage, ectopic pregnancy, and live birth.

1.3 Ovarian Stimulation Protocols

Short-Acting Long Protocol: Starting on day 21 of the menstrual cycle, patients received short-acting GnRH agonist (GnRH-a) 0.1 mg daily for 14 days. Upon achieving downregulation criteria (FSH<5 U/L, LH<5 U/L, E2<50 ng/L, endometrial thickness <5 mm, and no functional cysts), gonadotropin (Gn) stimulation was initiated. When at least two leading follicles reached $ $18 mm diameter, or three leading follicles reached $ $17 mm with mean peripheral blood E2 $ $200 ng/L per follicle >14 mm, trigger was performed with either hCG 5,000-7,500 IU intramuscularly or Ovidrel 250 g subcutaneously, followed by oocyte retrieval 36 hours later.

Antagonist Protocol: Starting on menstrual cycle days 2-4, patients received Gn stimulation. When leading follicles reached 14 mm, GnRH antagonist (GnRH-ant) 0.25 mg was added once daily. Trigger criteria and timing were identical to the short-acting long protocol.

1.4 Propensity Score Matching

We performed 1:1 PSM using R 4.1.1 software, with COH protocol as the dependent variable (short-acting long protocol=0, antagonist protocol=1). Covariates included variables showing significant between-group differences at baseline (female age, BMI, baseline FSH, baseline LH, and AFC). Nearest-neighbor matching was employed with a caliper value of 0.2.

1.5 Cost-Effectiveness Analysis

Cost Calculation: Total costs comprised direct medical expenses for ovulation induction medications and other procedure-related fees (including oocyte retrieval, fertilization, and embryo transfer). Travel costs and lost wages were excluded due to lack of standardized measurement and relatively low contribution.

Outcome Measures: Serum hCG was measured two weeks after embryo transfer to confirm biochemical pregnancy. Positive cases underwent transvaginal ultrasound four weeks post-transfer to confirm clinical pregnancy. Final outcomes were categorized as non-pregnancy, ectopic pregnancy, miscarriage, or live birth.

Cost-Effectiveness Analysis: We used TreeAge Pro 2011 for analysis. The cost-effectiveness ratio (CER) represents cost per live birth, with lower values indicating better economic performance. The incremental cost-effectiveness ratio (ICER) was calculated as (Ci-Cc)/(Ei-Ec), where i denotes the intervention and c the comparator. We used one times China's 2018 per capita GDP (¥64,644) as the willingness-to-pay (WTP) threshold. Probabilistic sensitivity analysis

was performed using 1,000 Monte Carlo simulations, and a tornado diagram was generated for one-way sensitivity analysis.

1.6 Statistical Analysis

Categorical data were described using percentages and compared using R×C chi-square tests. Normally distributed continuous data were expressed as mean±SD and compared using independent t-tests. Non-normally distributed data were presented as median (P25, P75) and compared using Mann-Whitney U tests. Statistical significance was defined as $P<0.05$.

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2. Results

2.1 Baseline Characteristics Before and After PSM

Before PSM, significant differences existed between groups in female age, BMI, baseline FSH, baseline LH, and AFC ($P<0.05$). After PSM, 390 cycles were matched in each group, with no significant differences in these baseline characteristics ($P>0.05$) .

2.2 Treatment Indicators and Clinical Outcomes After PSM

Treatment Indicators: After PSM, the antagonist protocol group showed significantly lower Gn duration, total Gn dosage, trigger-day E2, endometrial thickness, retrieved oocyte count, and mature oocyte count, but higher trigger-day LH compared to the short-acting long protocol group ($P<0.05$) .

Clinical Outcomes: After PSM, the antagonist protocol group had significantly lower clinical pregnancy rate (43.08% vs. 54.62%, $P=0.001$), implantation rate (29.15% vs. 37.01%, $P=0.001$), and live birth rate (33.59% vs. 44.10%, $P=0.003$). No significant differences were observed in multiple pregnancy rate, ectopic pregnancy rate, or miscarriage rate ($P>0.05$) .

2.3 Direct Treatment Costs After PSM

After PSM, the antagonist protocol group had significantly lower median per-cycle ovulation induction drug costs and total costs compared to the short-acting long protocol group ($P<0.05$). Other procedure-related costs did not differ significantly between groups .

2.4 Cost-Effectiveness Analysis

Using live birth rate as the primary endpoint, the cost per live birth was ¥66,397.92 in the antagonist protocol group and ¥54,226.33 in the short-acting long protocol group. The ICER was ¥15,325.88, which is below the WTP threshold of one times China's 2018 per capita GDP (¥64,644), indicating that the short-acting long protocol is economically advantageous .

2.5 Sensitivity Analysis

The tornado diagram [Figure 1: see original paper] identified the four parameters with greatest impact on ICER: short-acting long protocol live birth rate (pAG_{LB}), antagonist protocol live birth rate (pAN_{LB}), short-acting long protocol other costs (cAG_{OT}), and short-acting long protocol medication costs (cAG_{MED}). Across all parameter ranges, ICER remained below the WTP threshold of ¥64,644. Probabilistic sensitivity analysis showed that the probability of the short-acting long protocol being more cost-effective increased with higher WTP values [Figure 2: see original paper]. At a WTP of three times per capita GDP (¥193,932), the short-acting long protocol had a 99% probability of being cost-effective. These findings confirm the robustness of our primary analysis.

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3. Discussion

Clinical decision-making in assisted reproduction increasingly incorporates treatment costs. This cost-effectiveness analysis of antagonist versus short-acting long protocols in fresh embryo transfer cycles provides evidence-based guidance for developing clinically effective and economically rational treatment strategies.

The short-acting long protocol is widely regarded as the standard COH regimen. Its pituitary downregulation enables synchronous follicular maturation under exogenous Gn stimulation, prevents premature LH surges, and improves clinical pregnancy rates, albeit with increased ovarian hyperstimulation syndrome risk due to higher Gn dosage. The antagonist protocol offers advantages including shorter duration, rapid action, lower medication requirements, and reduced ovarian hyperstimulation syndrome incidence, making it less costly and more convenient.

Our PSM-matched results show that the antagonist protocol group had significantly lower Gn duration, total Gn dosage, trigger-day E2, endometrial thickness, retrieved oocyte count, mature oocyte count, clinical pregnancy rate, implantation rate, and live birth rate, but higher trigger-day LH ($P<0.05$). These findings align with LAMBALK et al., who reported significantly lower ongoing pregnancy rates with antagonist protocols in the general population [RR=0.89, 95%CI (0.82, 0.96)], possibly due to inadequate suppression of premature LH surges causing asynchronous follicular development and reduced oocyte yield. Other studies suggest that agonist protocols may provide better endometrial receptivity than antagonist protocols, contributing to superior clinical outcomes.

Although the antagonist protocol group had significantly lower per-cycle medication and total costs ($P<0.05$), cost-effectiveness analysis using live birth rate as the endpoint demonstrated superior economic performance of the short-acting long protocol. One-way sensitivity analysis showed ICER remained below the WTP threshold across all parameter variations. Probabilistic sensitivity analy-

sis similarly demonstrated that the probability of the short-acting long protocol being more economical increased with higher WTP values, reaching 99% at three times per capita GDP (¥193,932). These results are consistent with BENBASSAT et al., who found agonist protocols had the highest live birth rate (34%) and lowest cost per live birth (5,033.51 lev) in a national-level Bulgarian study. JING Miaomiao reported that antagonist protocols had lower cost per ongoing pregnancy (¥110,989.38) than short-acting long protocols (¥130,160.66) when considering only fresh cycles, but short-acting long protocols remained more cost-effective (¥49,673.16 vs. ¥53,476.01) when cumulative ongoing pregnancy rates including frozen cycles were analyzed. The discrepancy with our findings may reflect differences in outcome measures (ongoing pregnancy vs. live birth) and lack of baseline balancing in that retrospective study.

PSM effectively simulated randomization and controlled for inter-group imbalances in confounding factors common to retrospective studies. By following patients to live birth—the ultimate goal of assisted reproduction—our study provides more meaningful results than those using clinical pregnancy as the endpoint. However, limitations include the single-center retrospective design, relatively small sample size, and restriction to fresh embryo transfer cycles. Multi-center, large-scale prospective studies are needed to validate these findings.

In conclusion, the short-acting long protocol demonstrates superior clinical and economic performance compared to the antagonist protocol in fresh embryo transfer cycles. Future health economics evaluations of additional COH protocols will further inform clinical decision-making and optimize resource allocation in assisted reproduction.

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Author Contributions: HUANG Taishuai contributed to study conception, design, implementation, data collection, statistical analysis, and manuscript writing; CHI Yan contributed to manuscript revision; HE Ping and HUANG Guolan contributed to data collection and organization; ZUO Yanli supervised study planning and execution, and was responsible for quality control, manuscript review, and overall accountability. All authors approved the final manuscript.

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[Figure 1: see original paper] **[Figure 2: see original paper]**

Note: Figure translations are in progress. See original paper for figures.