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Clinical Effects of the Follicular Phase Long Regimen and Luteal Phase Long Regimen on Ovulation Induction in IVF-ET Treatment: A Meta-Analysis

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Abstract: *Objective:* To systematically evaluate the clinical effects of the follicular phase long regimen and the luteal phase long regimen on ovulation induction in IVF-ET treatment. *Methods:* Databases including PubMed, Embase, Cochrane Library, CNKI, Chinese Biomedical Literature (CBM), VIP, Wanfang, and others were searched up to January 2021. Clinical studies on ovulation induction using the follicular phase long regimen and luteal phase long regimen in IVF-ET treatment were identified. Literature screening, data extraction, and quality evaluation were conducted based on inclusion and exclusion criteria. Meta-analysis was performed using RevMan 5.3 software. *Results:* After screening, a total of 11 studies were included, comprising 21,544 patients: 9,974 in the follicular phase long regimen group and 11,570 in the luteal phase long regimen group. The meta-analysis results were as follows: (1) The number of Gn days and the total amount of Gn in the follicular phase long regimen were higher than those in the luteal phase long regimen ($P < 0.05$); (2) The number of eggs obtained in the follicular phase long regimen was higher than that in the luteal phase long regimen ($P < 0.05$). There were no significant differences in the rate of embryo optimization and cycle cancellation between the two groups ($P > 0.05$); (3) The embryo implantation rate and clinical pregnancy rate in the follicular phase long regimen were higher than those in the luteal phase long regimen ($P < 0.05$), while the abortion rate in the follicular phase long regimen was lower than that in the luteal phase long regimen ($P < 0.05$). *Conclusion:* Compared to the luteal phase long regimen, the follicular phase long regimen involves more Gn days and a higher total amount of Gn. The optimal embryo rate and cycle cancellation rate were similar between the regimens, but the follicular phase long regimen resulted in more eggs, significantly improved the implantation and clinical pregnancy rates, and reduced the abortion rate. However, these conclusions require further validation through more multicenter, large-sample RCT studies.

Keywords: *In vitro* fertilization and embryo transfer (IVF-ET); Follicular phrase long regimen; Luteal phase long regimen; Meta-analysis

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1. Introduction

Since 1984, when Porter *et al*. [1] first reported the application of gonadotropin-releasing hormone agonist (GnRH-a) in in vitro fertilization-embryo transfer technology (IVF), it has been widely adopted due to its ability to downregulate the pituitary gland. This downregulation can improve the synchronization of follicular development, inhibit the premature rise of endogenous LH and progesterone in the late follicular stage, and result in the retrieval of more mature eggs. With advantages such as reducing the cycle cancellation rate and improving the clinical pregnancy rate, the GnRH-a downregulation protocol has become the preferred protocol in most reproductive centers in China [2].

The luteal phase long protocol is the classical method for pituitary downregulation, known for its stable pregnancy rates. In contrast, the long follicular phase protocol is primarily used for patients with endometriosis. However, in recent years, with the increased clinical application of the long follicular phase protocol, domestic studies have indicated that its clinical outcomes are better than those of the long luteal phase protocol [3,4]. Conversely, foreign studies have shown no significant difference in clinical outcomes between the two protocols [5].

Therefore, this study conducted a meta-analysis by comparing the clinical effects of the follicular phase long protocol and the luteal phase long protocol in IVF-ET treatment. The aim was to provide a basis for selecting the most effective ovulation induction regimen for infertility patients.

2. Materials and methods

2.1. Literature search

PubMed, Embase, Cochrane Library, China National Knowledge Network (CNKI), China Biomedical Literature (CBM), VIP, Wanfang, and other databases were searched electronically, covering publications up to June 2021. Chinese search terms included: in vitro fertilization-embryo transfer, intracytoplasmic sperm injection, IVF-ET, ICSI, controlled ovulation induction, agonist, long-term protocol, clinical outcome, pregnancy rate, live birth rate, etc. English search terms included: in vitro fertilization-embryo transfer, intracytoplasmic sperm injection, IVF-ET, ICSI, controlled ovarian hyperstimulation, GnRH-a, long protocol, clinical outcomes, pregnancy rate, live birth rate, etc.

Inclusion criteria included randomized controlled trials or clinical controlled trials involving infertile patients undergoing IVF/ICSI-ET treatment, where ovulation induction was performed using the long follicular phase regimen in the experimental group and the long luteal phase regimen in the control group. Exclusion criteria included duplicate publications, studies with missing data, case reports, and reviews.

2.2. Research methods

2.2.1. Literature selection and data extraction

EndNote software was used to manage the literature. Two researchers independently selected literature according to the inclusion and exclusion criteria, excluding irrelevant studies by reviewing titles and abstracts. Full texts were then read to determine inclusion. Discrepancies were resolved through discussion. Data extracted included:

(1) Basic information: first author, study year, country, sample size, age, protocol type, etc.

(2) Outcome indicators: Gn days, total Gn, number of eggs harvested, optimal embryo rate, cycle cancellation rate, embryo implantation rate, clinical pregnancy rate, and abortion rate.

2.2.2. Methodological quality assessment of included studies

Quality assessment was conducted independently by two authors using the risk assessment criteria from the Cochrane Handbook for Systematic Reviews of Interventions. Key criteria included random-sequence generation, allocation concealment, blinding of researchers and participants, blinding of outcome assessors, completeness of outcome reporting, selective reporting, and other biases. Studies were rated as follows:

(1) A: 7 items satisfied.

(2) B: at least 2 items satisfied.

(3) C: 1 item satisfied.

2.3. Statistical analysis

Meta-analysis was performed using RevMan 5.3 software. Heterogeneity was tested using the Q test and I^2 test. If $P > 0.1$ and $I^2 < 50\%$, studies were considered homogeneous, and a fixed-effects model was used. If $P < 0.1$ and $I^2 > 50\%$, studies were considered heterogeneous, and a random-effects model was used. Dichotomous variables were represented by odds ratio (OR) and 95% confidence interval (95% CI). Continuous variables were represented by standardized mean difference (SMD) and 95% CI.

3. Results

3.1. Search results and basic characteristics of included studies

A total of 1,844 articles were obtained from the databases: 619 from PubMed, 116 from Embase, 128 from the Cochrane Library, 268 from CNKI, 85 from CBM, 239 from VIP, and 389 from Wanfang. After removing duplicates and screening titles, abstracts, and full texts, 11 studies were included, encompassing a total of 21,544 patients. Of these, 9,974 patients were included in the follicle phase long regimen group, and 11,570 patients were included in the luteal phase long regimen group. The basic characteristics of the included studies are shown in **Table 1**.

Table 1. Basic characteristics of included studies

Research	Country	Total cases		Age (years)		Intervention measure	Outcome indicators
		Study group	Control group	Study group	Control group		
Abdulmagid Sarhan 2016 [6]	Egypt	66	115	34.6 ± 3.2	34.6 ± 3.8	(1) Follicular phase short-acting long regimen (2) Luteal phase short-acting long regimen	1–3, 5, 7
Robert F. Harrison 1996 [7]	Ireland	38	48	35.3 ± 3.6	35.1 ± 4.1	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1, 2, 5, 7
Yin Yisha 2020	China	4854	2811	30.37 ± 4.14	30.28 ± 4.25	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1–3, 7, 8
Chang Fan 2019	China	160	160	31.7 ± 3.5	31.2 ± 3.6	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1–3, 6–8
Julie 2019[9]	China	460	320	30.15 ± 5.12	30.49 ± 5.33	(1) Follicular phase long-acting long regimen (2) Luteal phase long-acting long regimen	1–3, 6–8

Table 1 (Continued)

Research	Country	Total cases		Age (years)		Intervention measure	Outcome indicators
		Study group	Control group	Study group	Control group		
Hu Linli 2016	China	2395	2802	30.95 ± 5.21	30.69 ± 5.24	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1, 3–8
Tan Qingying 2017 [10]	China	453	539	30.15 ± 5.51	30.51 ± 5.34	(1) Follicular phase long-acting long regimen (2) Luteal phase long-acting long regimen	1-3, 6–8
Tan Zhuo Jie 2020	China	170	177	31.41 ± 3.49	32.09 ± 3.61	(1) Follicular phase long-acting long regimen (2) Luteal phase long-acting long regimen	1–8
Tan Ying 2020	China	323	319	30.47 ± 3.86	30.83 ± 4.16	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1, 3, 4, 7, 8
Guo Peipei 2020	China	990	4230	31.26 ± 4.99	30.98 ± 5.26	(1) Follicular phase long-acting long regimen (2) Luteal phase short-acting long regimen	1–3, 6–8
Huang Qing 2002	China	65	49	31.5 ± 3.8	31.9 ± 3.8	(1) Follicular phase long-acting long regimen (2) Luteal phase long-acting long regimen	1–4, 7

Observation indicators: 1, Gn days; 2, total Gn; 3, number of eggs harvested; 4, fine embryo rate; 5, cycle cancellation rate; 6, rate of embryo implantation; 7, clinical pregnancy rate; 8, miscarriage rate.

3.2. Results of meta-analysis

(1) Gn days and total Gn: All 11 studies reported the number of Gn days. Heterogeneity analysis showed $I^2 = 97\%$, $P < 0.00001$, indicating significant heterogeneity. Combined analysis with a random-effects model showed that the days of Gn use in the long follicle phase group were greater than in the long luteal phase group [SMD = 1.18, 95% CI (0.71, 1.65), $P < 0.00001$] (**Figure 1**). Nine studies reported the total amount of Gn used, with heterogeneity analysis showing $I^2 = 95\%$, $P < 0.00001$, indicating significant heterogeneity. Combined analysis with a random-effects model showed that the total amount of Gn used in the long follicle phase group was greater than in the long luteal phase group [SMD = 154.06, 95% CI (4.11, 304.02), $P = 0.04$] (**Figure 2**).

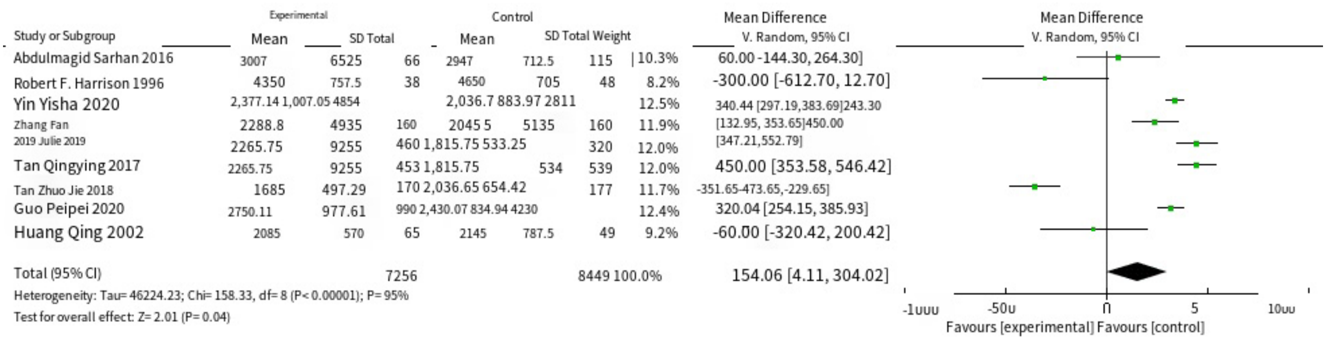

Figure 1. Meta-analysis of Gn days in follicular phase long regimen and luteal phase long regimen

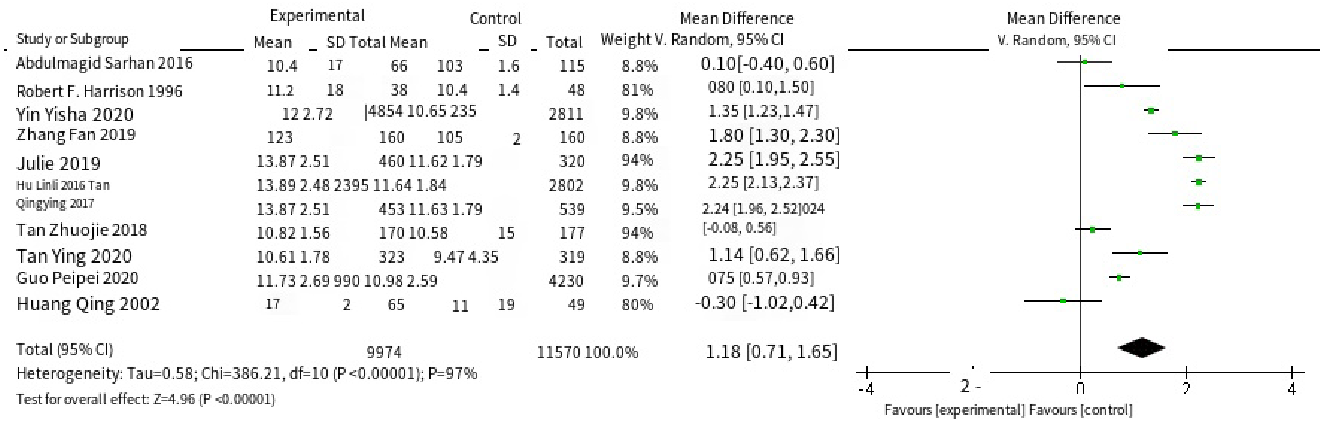

Figure 2. Meta-analysis of total Gn days of follicular phase long regimen and luteal phase long regimen

(2) Number of eggs harvested: Ten studies reported the number of eggs harvested, with heterogeneity analysis showing $I^2 = 93\%$, $P < 0.00001$, indicating significant heterogeneity. Combined analysis with a random-effects model showed that the number of eggs harvested in the long follicle phase group was higher than in the long luteal phase group [SMD = 1.23, 95% CI (0.38, 2.08), $P = 0.004$] (**Figure 3**).

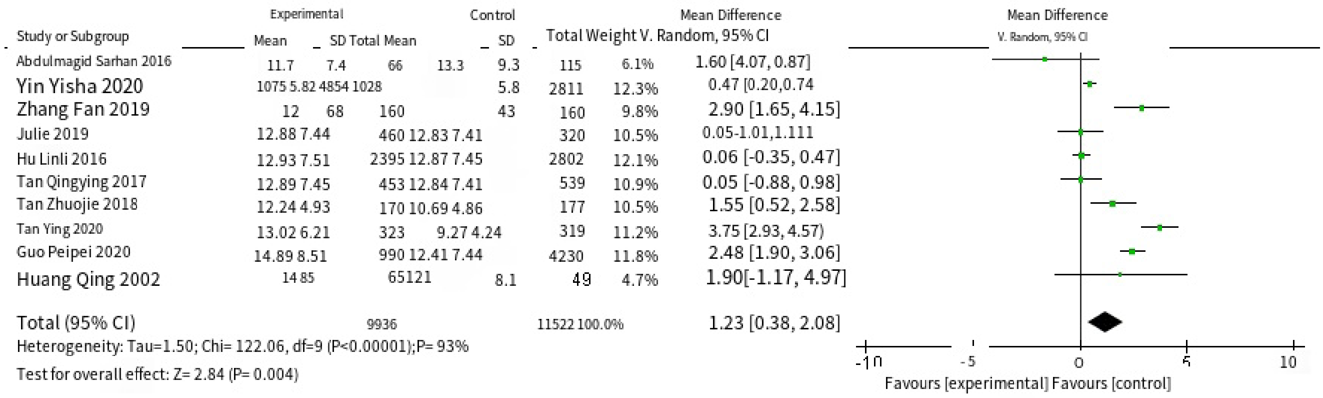

Figure 3. Meta-analysis of the number of eggs obtained by follicular phase long regimen and luteal phase long regimen

(3) Optimal embryo rate: Four studies reported the optimal embryo rate. Heterogeneity analysis showed $I^2 = 98\%$, $P < 0.00001$, indicating significant heterogeneity. Combined analysis with a random-effects model showed no significant difference in the optimal embryo rate between the long follicle phase and long luteal phase regimens [OR = 1.11, 95% CI (0.67, 1.84), $P = 0.68$] (**Figure 4**).

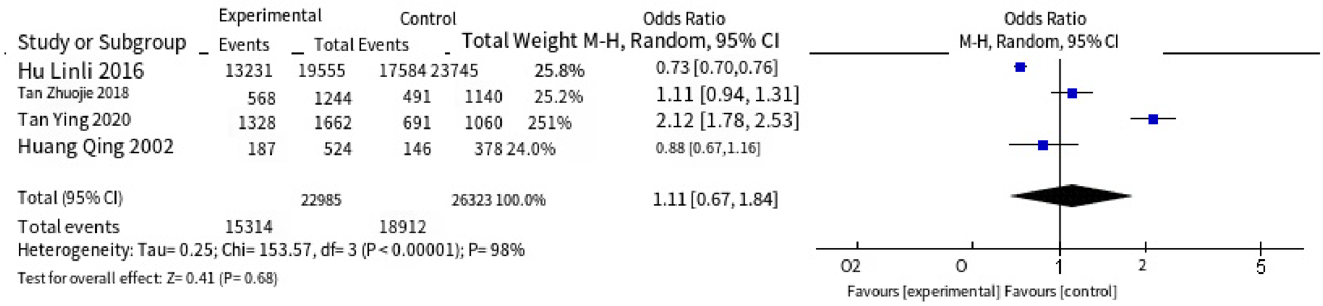

Figure 4. Meta-analysis of optimal embryo rate of follicular phase long regimen and luteal phase long regimen

(4) Cycle cancellation rate: Four studies reported cycle cancellation rates, with heterogeneity analysis showing I^2 = 56%, P = 0.08, indicating significant heterogeneity. Combined analysis with a random-effects model showed no significant difference in cycle cancellation rates between the long follicle phase and long luteal phase regimens [OR = 1.11, 95% CI (0.48, 2.54), P = 0.81] (**Figure 5**).

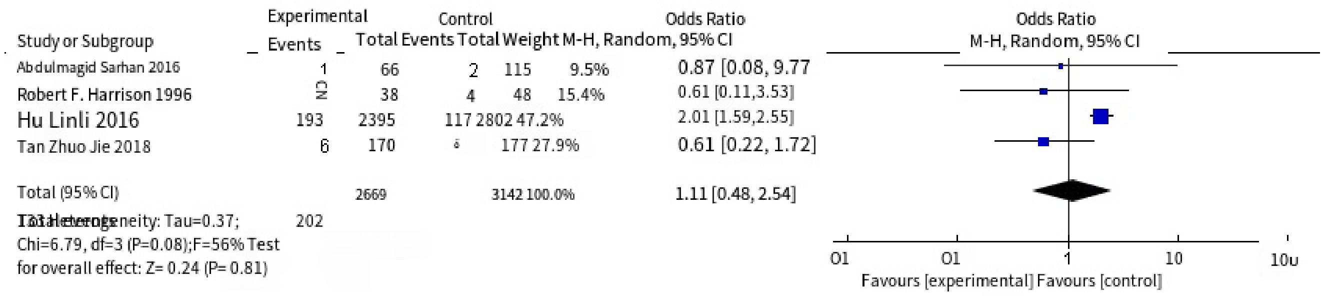

Figure 5. Meta-analysis of cycle cancellation rates of follicular phase long regimen and luteal phase long regimen

(5) Embryo implantation rate and clinical pregnancy rate: Six studies reported the embryo implantation rate, with heterogeneity analysis showing I^2 = 35%, P = 0.17, indicating no significant heterogeneity. Combined analysis with a fixed-effects model showed that the embryo implantation rate in the long follicle phase regimen was higher than in the long luteal phase regimen [OR = 1.45, 95% CI (1.35, 1.56), P < 0.00001] (**Figure 6**). Eleven studies reported the clinical pregnancy rate, with heterogeneity analysis showing I^2 = 51%, P = 0.03, indicating significant heterogeneity. Combined analysis with a random-effects model showed that the clinical pregnancy rate in the long follicle phase group was higher than in the long luteal phase group [OR = 1.45, 95% CI (1.28, 1.64), P < 0.00001] (**Figure 7**).

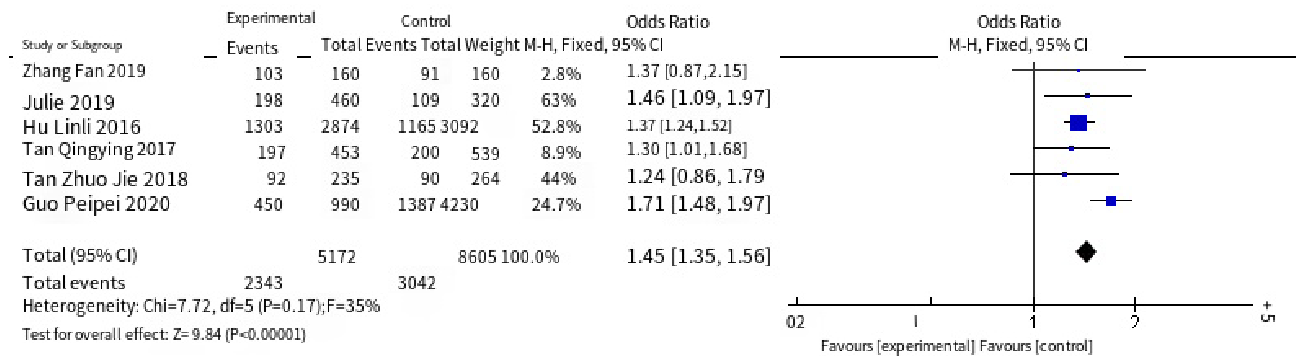

Figure 6. Meta-analysis of implantation rates of embryos with follicular phase long regimen and luteal phase long regimen

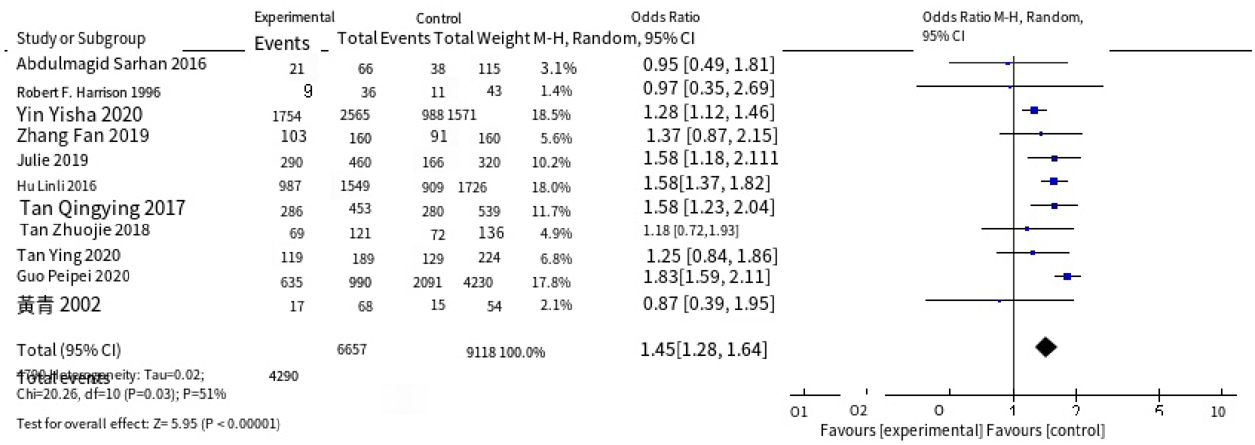

Figure 7. Meta-analysis of clinical pregnancy rate of follicular phase long regimen and luteal phase long regimen

(6) Miscarriage Rate: Eight studies reported the miscarriage rate. Heterogeneity analysis showed $I^2 = 0\%$, $P = 0.63$, indicating no significant heterogeneity. Combined analysis with a fixed-effects model showed that the miscarriage rate in the long follicle phase group was lower than in the long luteal phase group [OR = 0.71, 95% CI (0.61, 0.82), $P < 0.00001$] (**Figure 8**).

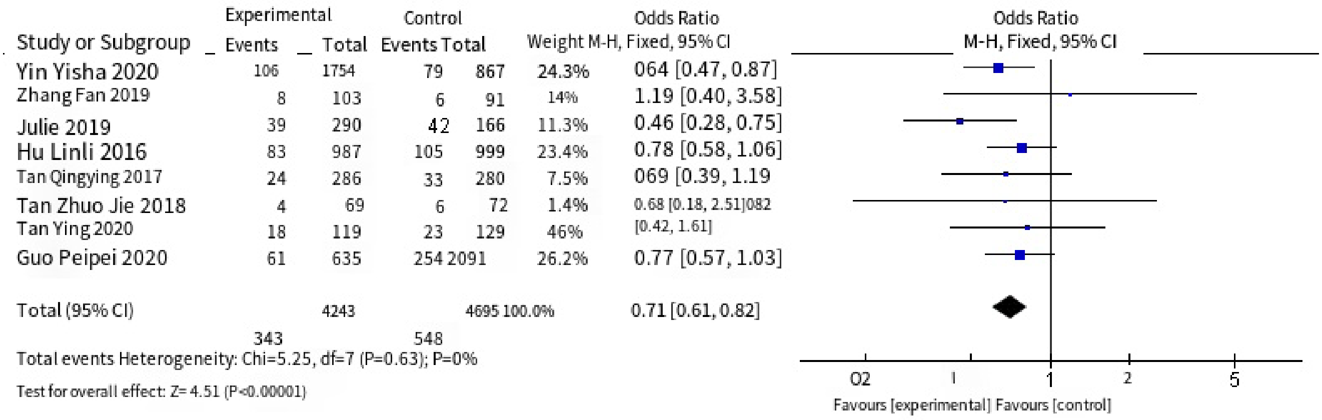

Figure 8. Meta-analysis of abortion rates in follicular phase long regimen and luteal phase long regimen

4. Discussion

Controlled ovarian hyperstimulation (COH) is crucial for improving IVF-ET outcomes. Pituitary down-regulation with GnRH-a, combined with exogenous Gn, induces the simultaneous development of an appropriate number of follicles and inhibits endogenous LH peaks. This prevents premature luteinization of follicles, leading to high-quality oocytes and embryos, thereby improving pregnancy outcomes. Based on the timing of GnRH-a administration, the protocols can be categorized into long follicular phase and long luteal phase regimens. The long luteal phase regimen is the mainstream protocol in most centers in China due to its rapid down-regulation and stable pregnancy rates [15]. However, with the accumulation of COH-related data, the clinical outcomes of the long follicular phase regimen seem more promising [3,4].

This study systematically evaluated the clinical effects of long follicular phase and long luteal phase regimens. It was found that the long follicular phase regimen resulted in higher Gn days, total Gn usage, and the number of eggs collected compared to the long luteal phase regimen. However, there was no significant difference in the optimal embryo rate and cycle cancellation rate between the two protocols. The implantation rate and clinical pregnancy rate were higher, and the miscarriage rate was lower in the long follicular phase regimen.

The inhibitory effect of GnRH-a on LH is dose-dependent [16]. The short-acting GnRH-a regimen for the long luteal phase is administered multiple times, or the long-acting GnRH-a is administered as a single dose of 1/3-1/2, resulting in a lighter inhibitory effect on the pituitary gland. The long follicular phase regimen uses a single full dose of long-acting GnRH-a, which has a deeper inhibitory effect on the pituitary gland, leading to an increase in Gn days and dosage. This finding is consistent with the results of Albuquerque *et al.* [17]. The increased administration days and Gn dosage significantly improve the egg acquisition rate and the number of mature eggs [18]. Chen *et al.* [19] also pointed out that prolonging the Gn administration time enhances FSH receptor activity, promoting more follicle development, which aligns with this study's results.

However, the effect of follicular phase and luteal phase regimens on the optimal embryo rate remains controversial. Raphael *et al.* [15] suggested that lower regulation during the follicular phase allows the ovary to respond better to exogenous Gn, resulting in more mature eggs and high-quality embryos, which was consistent with Tan *et al*.'s findings [11,12] in patients under 35 years old. Conversely, Hu *et al*. [4] argued that the long follicular phase regimen deeply inhibits LH levels, causing asynchronous follicle growth and a lower optimal embryo rate.

Embryo quality and endometrial receptivity are key determinants of IVF-ET success. Although there was no significant difference in the optimal embryo rate between the two regimens, the long follicular phase regimen had higher implantation and pregnancy rates and a lower miscarriage rate, likely due to improved endometrial receptivity. Yin [8] and Hu *et al*. [4] showed that endometrial thickness on HCG days was higher and estrogen levels were lower in the long follicular phase regimen compared to the long luteal phase regimen. Chen [20] and Gao [21] demonstrated that increased endometrial thickness correlates with higher pregnancy rates, while high estrogen levels can prematurely close the endometrial implantation window, reducing receptivity [22]. Edwards [23] believed that certain endometrial glands remain stationary for a period post-down-regulation, increasing pinopode processes and sensitivity to steroid hormones, thereby improving receptivity. Therefore, the long follicular phase regimen may enhance endometrial receptivity and pregnancy outcomes by extending down-regulation time and endometrial quiescence, reducing estrogen levels, and increasing endometrial thickness.

The results of this study indicated that the follicular phase long regimen had better outcome indicators, such as a higher number of eggs, improved implantation and pregnancy rates, and a lower miscarriage rate, compared to the luteal phase long regimen. Additionally, it could avoid ovarian cysts and pregnancy complications associated with GnRH-a injections in the long luteal phase regimen, making it one of the best protocols in clinical practice. However, some observational indicators in this meta-analysis showed significant heterogeneity, and these conclusions need to be validated by more large-sample, multicenter randomized controlled studies.

Disclosure statement

The authors declare no conflict of interest.

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