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Assessing the Effectiveness of Sequential Embryo Transfer in the RIF Patients

Xingnan Liu*, Na Zhang*

Department of Reproductive Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Research Article

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***For Correspondence:**
Xingnan Liu, Department of Reproductive Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China
Na Zhang, Department of Reproductive Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China
E-mail: 18134174257@163.com

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ABSTRACT

Purpose: This meta-analysis aims to evaluate the effectiveness of sequential embryo transfer (cleavage embryo transfer followed by blastocyst embryo transfer in the same cycle) in patients with repeated implant failure.

Methods: The search was performed in the English databases. The time range was from library building to August 20, 2023. Ultimately, the primary outcome measures were implantation rate and clinical pregnancy rate. The secondary indicators were miscarriage rate, multiple pregnancy rate, chemical pregnancy rate and ongoing pregnancy rate. The screening of articles was performed with Endnote, and data were analyzed with Review Manager 5.4.

Results: Our results showed that compared with control group, sequential embryo transfer was associated with higher implantation rate (RR=1.66, 95% CI: 1.34-2.05, P<0.00001, I2=0.0%) and clinical pregnancy rate (RR=1.58, 95% CI: 1.31- 1.91, P<0.00001, I2=18%). Groups did not differ statistically in miscarriage rate (RR=1.16, 90% CI: 0.64-2.10, P=0.62. The sequential group also did not show higher multiple pregnancy rate (RR=1.17, 90% CI: 0.80-1.72, P=0.42. Only two articles counted the chemical pregnancy rate and ongoing pregnancy rate, in which no differences were found (RR=1.17, 90% CI: 0.91-1.49, P=0.22; RR=0.79, 90% CI: 0.50-1.24, P=0.30). Only one article counted the live birth rate, thus preventing the meta-analysis and not yielding the live birth rate results for the sequential embryo transfer group.

Conclusion: Sequential embryo transfer contributes to higher implantation rate and clinical pregnancy rate in RIF patients, which is instructive for

future clinical work.

Keywords: Sequential embryo transfer; Repeated implantation failure; Assisted reproductive techniques; *In vitro* fertilization

INTRODUCTION

RIF is commonly defined as the inability to achieve a clinical pregnancy after transferring a minimum of four high-quality embryos during at least three fresh or frozen cycles in women under 40 years old [1,2] . Embryo implantation is a complex process that depends on three key factors: The health and quality of the embryo, the development of the endometrium, and the synchrony of both developments. High-quality embryos need to attach and invade a fully decidualized endometrium to achieve a successful pregnancy [3]. *In Vitro* Fertilization/Intracytoplasmic Sperm Injection and Embryo Transfer (IVF/ICSI-ET) consider endometrial receptivity as an important factor. Studies have shown that the implantation of embryos can induce better endometrial receptivity in mouse experiments [4]. With the evolution of Assisted Reproductive Technologies (ART), blastocyst embryos transfer has become effective in improving endometrial synchronization and achieving a higher success rate in IVF treatment. The Window of Implantation (WOI) refers to the specific time period when the endometrium is suitable for embryo implantation [5]. Prolonged embryo culture may improve pregnancy outcomes due to blastocyst transfer being more similar to natural cycles [6]. Blastocyst stage embryos are associated with higher euploid embryos compared to cleavage stage embryos, resulting in higher implantation rates and pregnancy rates [7-10]. Therefore, selecting the most promising embryos reaching the blastocyst stage for transfer is recommended. Embryo transfer is usually selected on day-3 (cleavage stage) or day-5 (blastocyst stage). Sequential embryo transfer, defined as cleavage embryo transfer first followed by blastocyst transfer in the same cycle, has been a topic of controversy [11]. A retrospective study demonstrated that sequential embryo transfer achieved higher pregnancy rates and multiple birth rates compared to day-3 cleavage transfer [12]. Another retrospective study involving 2836 cycles of frozen embryo transfer reported that sequential embryo transfer had higher clinical pregnancy rates, live birth rates, and implantation rates [13]. However, some studies did not observe an improvement in pregnancy rates with sequential transfer [14,15]. Therefore, the aim of this meta-analysis is to investigate the effect of sequential embryo transfer on pregnancy outcomes in patients with Recurrent Implantation Failure (RIF).

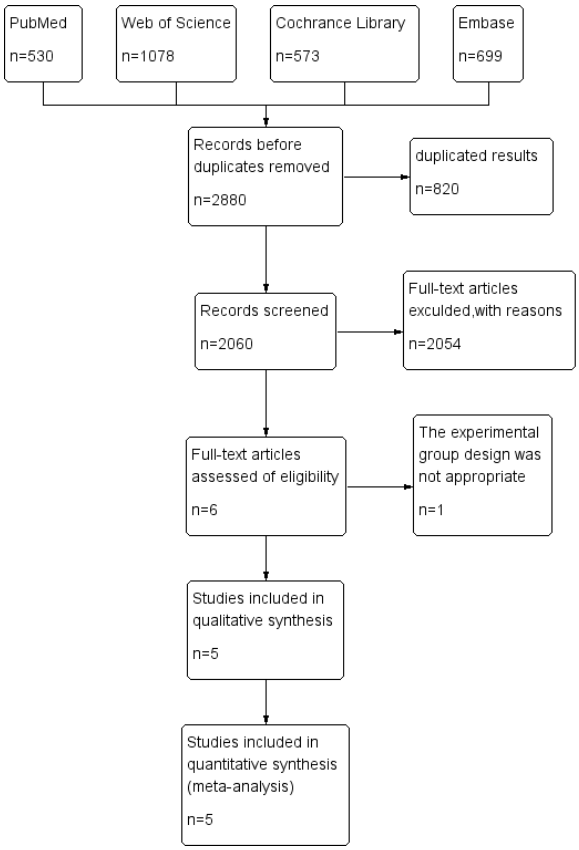
MATERIALS AND METHODS

This article passed the ethical review of both internal and internal peers. This study was conducted in strict compliance with the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) [16]. This meta-analysis was already registered on the PROSPERO website and was available under the registration ID (CRD42023448104).

Search strategy

Articles included in this Meta analysis are identified by searching the PubMed, Web of Science, Cochrane Library and Embase databases (The specific screening process is shown in Figure 1). The search scope was limited to the English-language articles. We used a combination of subject words and free words to search. The following term was used in this search: “Embryo transfer”, “Sequential embryo transfer”, “Embryo implantation”, “Repeated implantation failure”, “Recurrent implantation failure”, “Randomized controlled trial.” (Detailed search terms and strategies were provided in Supplementary Material).

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram.



Selection criteria

Two researchers independently screened the derived literature, and unrelated results were excluded. Included articles needed to meet the following criteria:

1. The study was a randomized controlled study;
2. All those included in the study were the RIF patients;
3. The intervention was sequential embryo transfer. Other articles with missing data or articles not providing sufficient information were excluded.

Date extraction

Two researchers extracted the data from the included literature, including first author, country and publication year, total number of included populations, average age, RIF inclusion criteria and pregnancy outcomes. Quality evaluation of the articles was performed using the Cochrance Scale.

Statistical analysis

We used the Review Manager 5.4 for the statistical analysis, Risk Ratio (RR) and 95% Confidence Interval (CI) were calculated. $P<0.05$ was considered statistically significant. And the statistical heterogeneity was determined by the I2. $I2 \geq 50\%$ is indicated statistical heterogeneity.

RESULTS

Baseline characteristics of the included studies

Through our search terms, 2880 articles were retrieved. 820 duplicates and 2,045 inconsistent articles were screened out after reading the titles and abstracts. Five RCT studies were finally included through reading the full text of the six articles. A total of 873 RIF patients were finally included, in which 405 patients underwent the sequential embryo transfer. The baseline characteristics of these five articles were presented (Table 1). The quality

evaluation of the article performed through the Cochrance Scale. (Graph was provided in the Supplementary Material as shown in Table 1.

Table 1. Characteristics of the included articles.

Study	Location	Patients (Sequential/Control)	Age (year)	Fresh/Frozen embryo transfer	Sequential embryo transplantation protocol	Reported outcomes
Saghar[11], 2023	Iran	202 (102/100)	33.92 ± 0.48	Fresh embryo cycle	D-3 and D-5	IR, CPR, MPR, MR, OPR, Chemical pregnancy rate
Haitham[17], 2020	Cairo, Egypt	204 (69/135)	32.30 ± 5.10	Fresh embryo cycle	D-3 and D-5	IR, CPR, MPR, MR, LBR
Ensieh[15], 2019	Iran	120 (60/60)	35.03 ± 4.35	Fresh embryo cycle	D-3 and D-5	CPR, MPR, Chemical pregnancy rate
Soheila[18], 2022	Iran	200 (100/100)	35.06 ± 4.33	Froze embryo cycle	D-3 and D-5	IR, CPR, MPR, MR
Wael A[19], 2015	Cairo, Egypt	147 (74/73)	34.40 ± 1.40	Fresh embryo cycle	D-3 and D-5	IR, CPR, MPR, MR, OPR

Note: D-3: Cleavage-stage embryo transfer on day 3, D-5: Blastocyst-stage embryo transfer on day 5, IR: Implantation Rate, CPR: Clinical Pregnancy Rate, MPR: Multiple Pregnancy Rate, MR: Miscarriage Rate, OPR: Ongoing Pregnancy Rate, LBR: Live Birth Rate.

Primary outcomes

The article aims to evaluate the effectiveness of sequential embryo transfer in patients with RIF. All five studies had mentioned the clinical pregnancy rate, and we found that the CPR was significantly increased in the sequential transplant group as compared to the control group (RR=1.58, 90% CI: 1.31- 1.91, P<0.0001, I2=18% (Figure 2). Four studies mentioned implantation rate, and the sequential group was found to be associated with a higher implantation rate by (RR= 1.54, 90% CI: 1.26- 1.88, P< 0.0001, I2= 0%) as shown in Figures 2 and 3.

Figure 2. Meta-analysis of Clinical Pregnancy Rate (CPR).

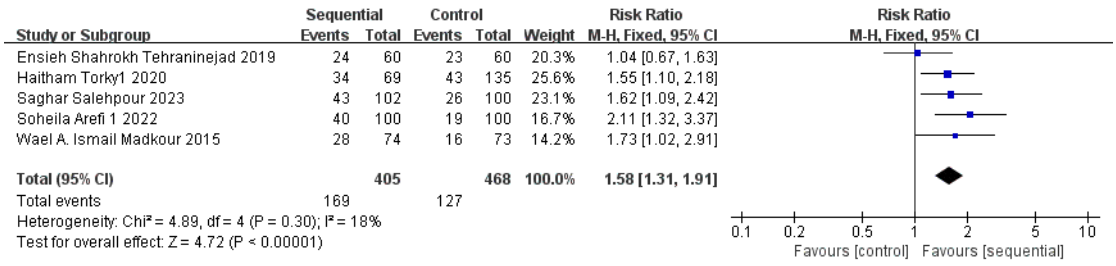
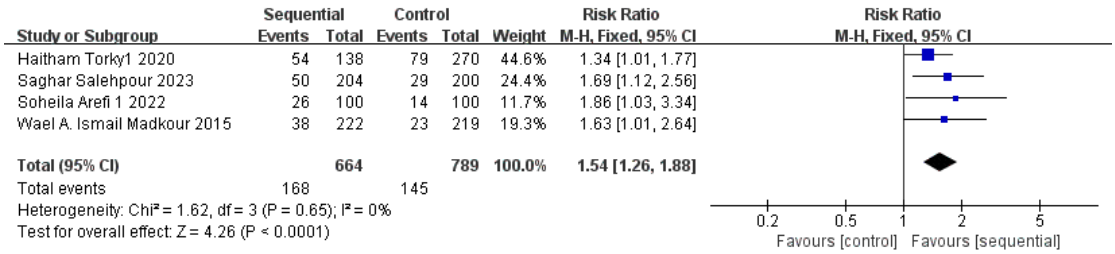


Figure 3. Meta-analysis of Implantation Rate (IR).



Secondary outcomes

Regarding secondary outcomes, the miscarriage rate, multiple pregnancy rate, chemical pregnancy rate and ongoing pregnancy rate were calculated, and there was no statistically significant difference in these outcomes between two groups (P>0.05). Groups did not differ statistically in miscarriage rate (RR=1.16, 90% CI: 0.64-2.10, P=0.62), (Figure 4). The sequential group also did not show higher multiple pregnancy rate (RR=1.17, 90% CI: 0.80-1.72, P=0.42), (Figure 5). Only two articles counted the chemical pregnancy rate and ongoing pregnancy rate, in which no differences were found (RR=1.17, 90% CI: 0.91-1.49, P=0.22), (Figure 6); (RR= 0.79, 90% CI: 0.50-1.24, P=0.30, Figure 7). Only one article counted the live birth rate, thus preventing the meta-analysis and not yielding the live birth rate results for the sequential embryo transfer group as shown in (Figures 4-7)

Figure 4. Meta-analysis of Miscarriage Rate (MR).

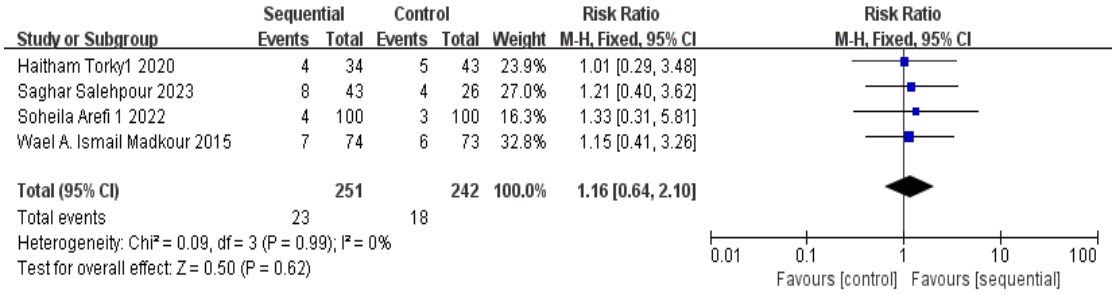


Figure 5. Meta-analysis of Multiple Pregnancy Rate (MPR).

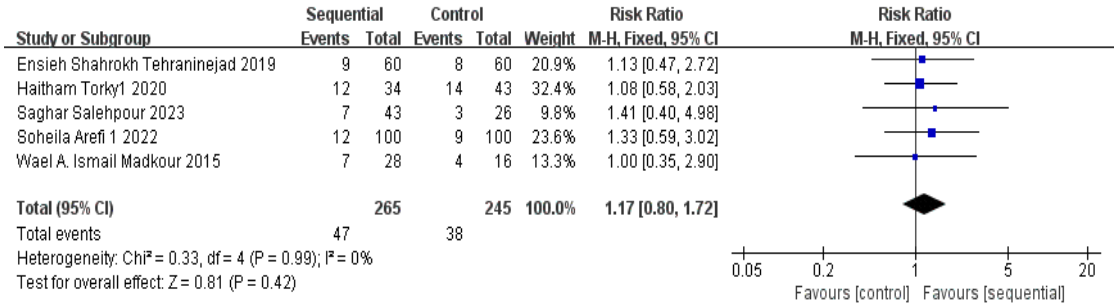


Figure 6. Meta-analysis of chemical pregnancy rate.

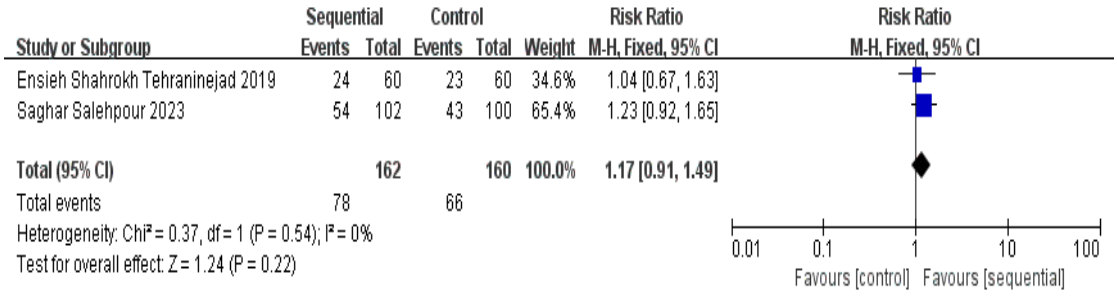
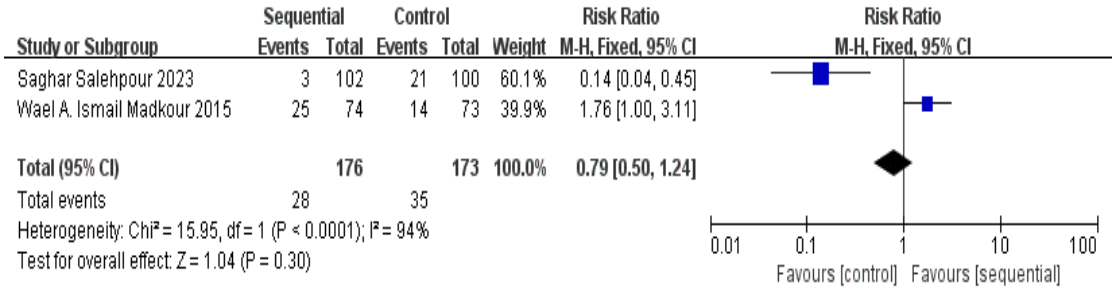


Figure 7. Meta-analysis of Ongoing Pregnancy Rate (OPR).



DISCUSSION

With the development of ART, the pregnancy rate of IVF/ICSI has gradually increased. However, RIF is still a major challenge for ART technology [20]. Previous studies had shown that sperm factors, genetics, hormonal abnormalities, disease susceptibility and autoimmune diseases were all the causes of RIF [21]. We know that the successful pregnancy depends on a higher endometrial receptivity, which is known as the Window of Implantation (WOI) [5,15]. Studies have shown that the WOI was displaced, and more than 75% of the patients last less than 48 hours [22]. The patients underwent either customized embryo transfer can obtain a higher pregnancy rate. Therefore, we believe that sequential transplantation can overcome the problem of WOI displacement by adjusting the timing of embryo transfer. Earlier transplanted can cleavage stage embryos regulate the immune tolerance of the mother and the fetus, inhibite the inflammatory response, and create a higher endometrial environment to facilitate the implantation of blastocyst stage embryos, explaining the higher implantation rate and clinical pregnancy rate of sequential transplantation [23].

Multiple pregnancies are directly related to the number of embryos transferred, and elective single embryo transfer can increase the cumulative clinical pregnancy rate and avoid multiple pregnancies compared with double embryo transfer [24]. However, our results did not find the statistically difference in the multiple pregnancy rate in two groups, which may be attributed to the impaired endometrial receptivity and activation of endometrial immune cells and immune factors [25].

CONCLUSION

The meta-analysis concluded that sequential embryo transfer can significantly improve implantation and clinical pregnancy rates in RIF patients, which will be instructive for the future clinical work. The limitation of this article was the failure to count Live Birth Rate (LBR). And only two articles counted the persistent and biochemical pregnancy rate, which showing high heterogeneity. Moreover, the women we included were all with good ovarian response and multiple high-quality embryos, so these results were not suitable for patients with poor ovarian response. In addition, the included RCT articles and the sample size were limited, and more higher-quality prospective randomized controlled studies with the larger sample size were expected.

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CONFLICTS OF INTEREST

It is stated that this article had no potential or actual conflict of interest with any institution or individual.

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