Comparison of Clinical Pregnancy Success Rates Between Fresh Embryo Transfer and Frozen Embryo Transfer in In Vitro Fertilization (IVF) at RSIA Bunda Jakarta from January 2020 to July 2020

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Abstract

The infertility rate in Indonesia is relatively high, therefore many people need further assistance in achieving pregnancy. In Vitro Fertilization (IVF) is a reproductive technology that has been one of the top choices. There are two methods of embryo transfer in the process, namely fresh embryo transfer and frozen embryo transfer. Based on conducted studies, the clinical pregnancy rate varies between studies. This study aimed to compare the clinical pregnancy success rates between fresh embryo transfers and frozen embryo transfers at RSIA Bunda Jakarta between January 2020-July 2020. The comparative analytic method is used with a cross-sectional study approach. The sample used is the medical records of all patients who underwent in vitro fertilization (IVF) with fresh embryo transfer or frozen embryo transfer methods at RSIA Bunda Jakarta from January 2020 to July 2020. The variable studied was the clinical pregnancy success rate in both transfer methods. Statistical test was done with SPSS by chi-square method to see the significance of the difference. The result of this study shows that the difference in clinical pregnancy success rate between the two embryo transfer methods was 6.91% with p = 0.176, therefore it is considered not significant. Insignificant results can be influenced by many factors, such as the large difference in sample size between the two methods of embryo transfer and the wide range of individual factors. Thus it is concluded that the difference in clinical pregnancy success rates between the two methods of embryo transfer is not significant enough to determine that frozen embryo transfer is a superior method of embryo transfer.

Keywords : IVF; Fresh Embryo Transfer; Frozen Embryo Transfer; Clinical Pregnancy

Background

Infertility is a condition in the reproductive system of either males or females that is characterized by the failure to achieve pregnancy after 12 months or more of regular sexual intercourse without contraception (WHO, 2020). The rate of infertility in Indonesia is still relatively high, around 10%-15% among 40 million couples of reproductive age facing fertility issues. According to data from the Central Statistics Agency in 2011, out of a total population of 237 million in Indonesia, there are approximately 39.8 million women of reproductive age, and 10-15% of them are reported to be unable to conceive or are infertile. In other words, it can be estimated that around 4 to 6 million couples in Indonesia require further assistance to conceive (Noveriyanti et al., 2017).

As one of the solutions to increase the success of pregnancy chances, assisted reproductive technology, namely in vitro fertilization (IVF), is currently recognized and has become one of the choices for infertile couples in Indonesia. In vitro fertilization (IVF) is a fertilization process where sperm is combined with an egg outside the woman's body, or in vitro (Kusuma, 2017). This method is increasingly being used as an option by the community to conceive in cases of infertility or for personal choice. According to data from the Indonesian In Vitro Fertilization Association (PERFITRI), the total number of IVF program cycles in Indonesia has surpassed 10,000 programs (PERFITRI, 2020).

In general, IVF has been trusted and widely practiced by Indonesians as an infertility solution, but the success rate of pregnancy from fresh embryo transfer remains relatively low to date (Liang et al., 2017). Based on previous research, the success rate of pregnancy through this method is only about 29.05% (Shi et al., 2017). Similar results were also found in another study conducted at an infertility clinic in Denpasar, with a success rate of 30.8% (Dhyani et al., 2020). The low success rate can be attributed to several factors, such as poor embryo quality, asynchronous interaction between the endometrium and the embryo, and inadequate endometrial receptivity. Endometrial receptivity is responsible for about 60% of implantation failures (Shi et al., 2017).

With the advancement of technology, the frozen embryo transfer method has emerged, offering several success factors that can minimize the implantation failure factors in fresh embryo transfer. Factors such as post-extraction and ovarian stimulation body conditioning (Weinerman and Mainigi, 2014), preimplantation chromosome abnormality testing (Liu, Su, and Wang, 2016) and timing adjustments for transfer (Mackens et al., 2017) are some factors that can minimize this implantation failure. This transfer method is often used for patients who fail to conceive using the fresh embryo transfer method (Maheswari et al., 2018). Some indications for performing frozen embryo transfer include reducing the risk of ovarian hyperstimulation syndrome (OHSS) (Bodri et al., 2010; Manzanares et al., 2010), endometrial anomalies (Venetis et al., 2013; de Ziegler et al., 2016), and implementing preimplantation genetic testing (Evans et al., 2014; Rodriquez-Purata et al., 2016; ESHRE PGT Consortium Steering Committee, et al., 2020).

Although the frozen embryo transfer method is expected to minimize implantation failure factors compared to fresh embryo transfer, the clinical pregnancy success rates reported by various studies show uncertain or insignificant outcomes related to the supposedly superior transfer method (Shi et al., 2018). The discrepancies in research outcomes regarding clinical pregnancy success rates pose a challenge in determining the best course of action for infertile couples in choosing an embryo transfer method. Therefore, patients require more up-to-date references as decision-making tools. In reality, recent research comparing the success rates of frozen embryo transfer and fresh embryo transfer in humans in Indonesia is still scarce. The lack of reference material for consideration can create feelings of uncertainty among patients regarding the outcomes of IVF. This uncertainty is one of the major psychological burdens for patients and can be a significant reason for discontinuing IVF therapy (Domar et al., 2018). Such uncertainty also amplifies the financial burden on patients (Rothwell et al., 2020), given the relatively high cost of IVF procedures. At times, medical professionals also face dilemmas when recommending embryo transfer methods to patients (Guo et al., 2020).

Several similar studies that have been conducted regarding the success rates of both transfer methods have yielded different results. According to research conducted by the American Society of Reproductive Medicine in 2013, involving women without specific conditions, the frozen embryo transfer method had a higher clinical pregnancy success rate than the fresh embryo transfer method (Roque et al., 2013). Similar findings

were also obtained in a study by Shandong University in 2020, which focused on women with thin endometrial lining. The clinical pregnancy success rate for frozen embryo transfer was 38.7% (67 out of 173), while for fresh embryo transfer, it was only 25.4% (44 out of 173) (Guo et al., 2020). However, in research conducted by the Massachusetts Medical Society in 2018, there was no significant difference in the clinical pregnancy success rates between the frozen embryo transfer and fresh embryo transfer methods. The clinical pregnancy success rate for fresh embryo transfer in this study was 54.4%, while for frozen embryo transfer, it was 56.9%. The small difference between these two results was not significant enough to determine which method was superior (Shi et al., 2018).

The low pregnancy rate with fresh embryo transfer, the psychological burden of insufficient reference material on patients, and the varying outcomes of similar studies conducted on clinical pregnancy success rates are the motivations behind the initiation of this research. The most recent data from both transfer methods will be compared and analyzed to determine which method has the highest clinical pregnancy success rate in this study. The data used will be sourced from fertility clinics in Indonesia, with the hope that common backgrounds and biological characteristics can broadly serve as more suitable references and considerations for infertile couples in Indonesia

Material and Methods

This study aimed to compare the clinical pregnancy success rates between fresh embryo transfers and frozen embryo transfers at RSIA Bunda Jakarta between January 2020 and July 2020. The research method used in this study is a comparative analytical approach using a cross-sectional study design. The purpose of comparative analysis is to examine the comparison between two or three factors by looking at their causes. A cross-sectional study is research conducted without any treatment to the respondents, and its aim is to investigate the presence or absence of a relationship between independent and dependent variables, where both types of variables are observed simultaneously at the same time (Rahmawati, Nursalam, and Kurniawati, 2014).

In this study, the sample used consists of the medical records of all patients who underwent in vitro fertilization (IVF) with fresh embryo transfer and frozen embryo transfer at RSIA Bunda Jakarta. Exclusion criteria include (1) Medical records of patients with endometrial wall thickness <6 mm (thin endometrial lining). (2) Medical records of patients with low embryo quality on the day of transfer. The sampling technique used in this study is the total sampling technique. Total sampling is a sampling technique where the sample size is equal to the population size. This technique was chosen because the number of fresh embryo transfer procedures performed from January 2020 to July 2020, which met the criteria, was estimated to be less than 100, and the number of such procedures was significantly lower compared to frozen embryo transfers.

Data analysis was conducted to determine the level of clinical pregnancy success in the fresh embryo transfer and frozen embryo transfer methods. After obtaining the data, data processing, coding, and tabulation were carried out. Initial data processing, labeling, and tabulation were performed using Microsoft Excel to organize the data. Statistical data processing was carried out using computerized SPSS software for Windows, employing the Chi-Square method in which P-value <0.05 indicates a significant difference and P-value >0.05 indicates no significant difference between the two methods of embryo transfer.

Results

Table 1. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer

Embryo Transfer Method	Total Number of Procedures	Number of Clinical Pregnancy	Clinical Pregnancy Rate (n%)
Fresh Transfer	1	2	44,79
Frozen Transfer	3	4	51,7
			Difference = 6,91

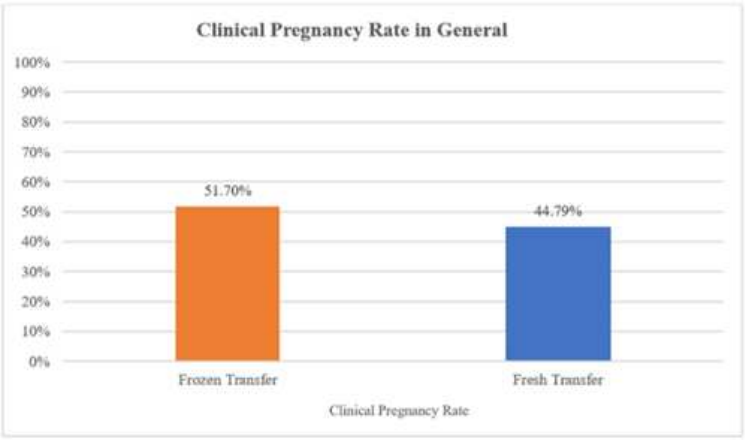

Figure 1. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer

Table 2. Statistical Analysis with Chi-square

Clinical Pregnancy Rate of Frozen Embryo Transfer	Clinical Pregnancy Rate of Frozen Embryo Transfer	Difference	P-Value
51,7%	44,79%	6,91%	0,176

Table 3. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Day of Transfer

Day of Transfer	Clinical Pregnancy Rate (n%) of Fresh Embryo Transfer	Clinical Pregnancy Rate (n%) of Frozen Embryo Transfer	Difference (n%)
D3	12 Successes / 29 Procedures = 41,38	12 Successes / 36 Procedures = 33,33	8,05
D5	31 Successes / 67 Procedures = 46,27	140 Successes / 258 Procedures = 54,26	7,99

Figure 2. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Day of Transfer

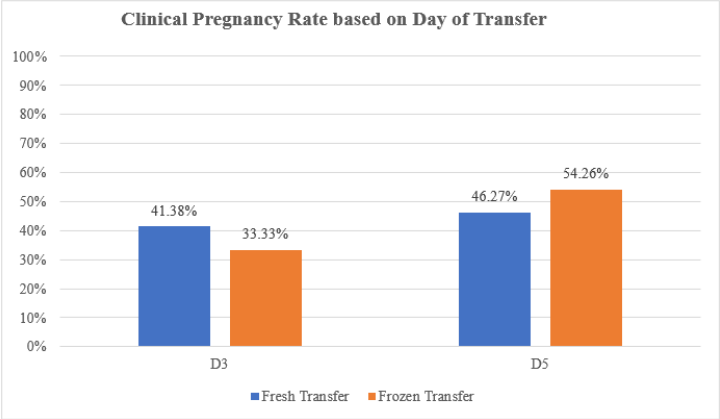

Table 4. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Maternal Age

Maternal Age	Clinical Pregnancy Rate (n%) of Fresh Embryo Transfer	Clinical Pregnancy Rate (n%) of Frozen Embryo Transfer	Difference (n%)
25-29	9 Successes / 18 Procedures = 50	14 Successes / 20 Procedures = 70	20
30-34	21 Successes / 36 Procedures = 58,33	60 Successes / 113 Procedures = 70	5,23
35-39	10 Successes / 28 Procedures = 35,71	50 Successes / 100 Procedures = 50	14,29
40-44	3 Successes / 12 Procedures = 25	26 Successes / 51 Procedures = 50,98	25,98
45-49	0 Successes / 2 Procedures = 0	2 Successes / 10 Procedures = 20	20

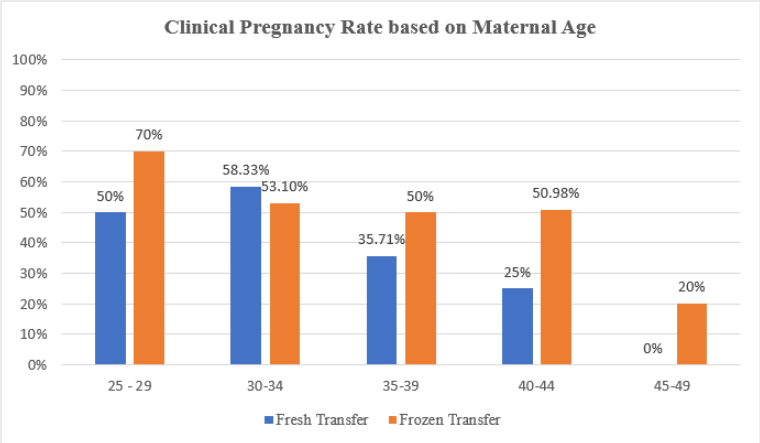

Figure 3. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Maternal Age

Table 5. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Duration of Infertility

Duration of Infertility (Years)	Clinical Pregnancy Rate (n%) of Fresh Embryo Transfer	Clinical Pregnancy Rate (n%) of Frozen Embryo Transfer	Difference (n%)
1-5	28 Successes / 58 Procedures = 48,28	80 Successes / 160 Procedures = 50	20
6-10	12 Successes / 25 Procedures = 48	56 Successes / 100 Procedures = 56	5,23
11-15	3 Successes / 11 Procedures = 27,27	16 Successes / 29 Procedures = 55,17	14,29
16-20	0 Successes / 2 Procedures = 0	0 Successes / 5 Procedures = 0	0

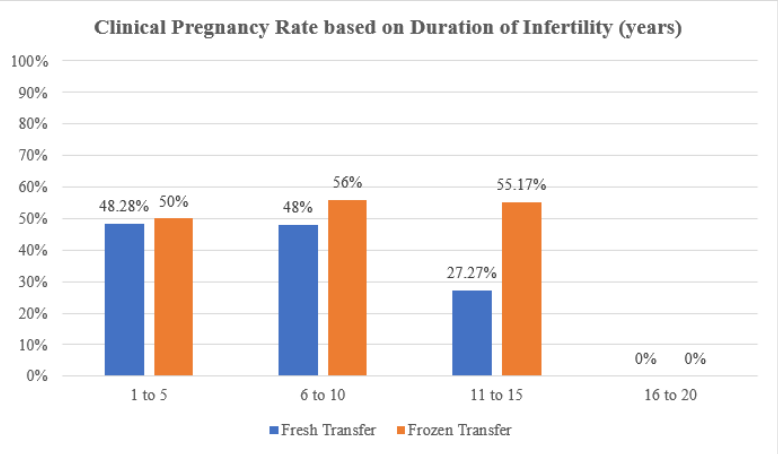

Figure 4. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Duration of Infertility

Table 6. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on IVF Indication

IVF Indication	Clinical Pregnancy Rate (n%) of Fresh Embryo Transfer	Clinical Pregnancy Rate (n%) of Frozen Embryo Transfer	Difference (n%)
Female Only	6 Successes / 16 Procedures = 37,5	26 Successes / 55 Procedures = 47,27	9,77
Male Only	13 Successes / 27 Procedures = 48,15	36 Successes / 75 Procedures = 48	0,15
Female & Male	3 Successes / 7 Procedures = 42,86	4 Successes / 11 Procedures = 55,17	6,5
Unexplained	6 Successes / 16 Procedures = 37,5	54 Successes / 95 Procedures = 56,84	19,34
Repeated Failure of IUI	0 Successes / 2 Procedures = 0	-	-

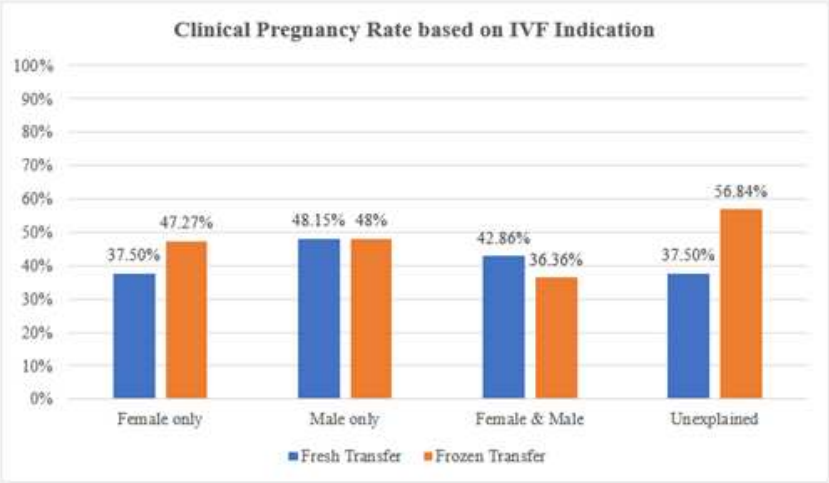

Figure 5. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on IVF Indication

Table 7. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Endometrial Thickness

Endometrial Thickness (mm)	Clinical Pregnancy Rate (n%) of Fresh Embryo Transfer	Clinical Pregnancy Rate (n%) of Frozen Embryo Transfer	Difference (n%)
6-7.9 mm	3 Successes / 5 Procedures = 60	26 Successes / 55 Procedures = 47,27	10
8-9.9 mm	10 Successes / 30 Procedures = 33,33	36 Successes / 75 Procedures = 48	13,82
10-11.9 mm	15 Successes / 35 Procedures = 42,86	4 Successes / 11 Procedures = 55,17	14,91
≥12 mm	15 Successes / 26 Procedures = 57,69	24 Successes / 45 Procedures = 53,33	4,36

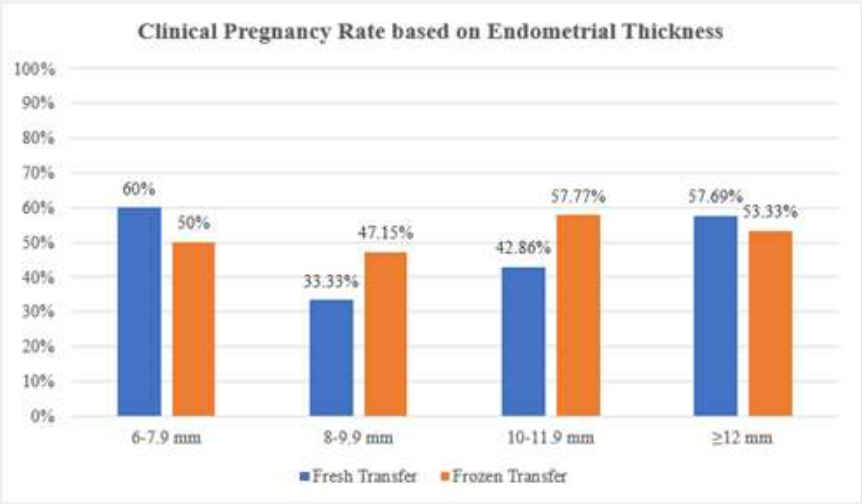

Figure 6. Comparison Chart of Clinical Pregnancy Success Rates in Fresh Embryo Transfer and Frozen Embryo Transfer based on Endometrial Thickness

a. Clinical pregnancy rate based on methods

The total number of frozen embryo transfer procedures from January 2020 to July 2020 was 294, with a clinical pregnancy success rate of 152, resulting in a success rate of 51.7%. The total number of fresh embryo transfer procedures during the same period was 96, with a clinical pregnancy success rate of 43, resulting in a success rate of 44.79%. There was a difference of 6.91% in the clinical pregnancy success rate between the two embryo transfer methods (Figure 1). In statistical analysis using the Chi-Square method, a P-value of 0.176 was obtained (<0.05) (Table 2).

b. Clinical pregnancy rate based on the day of transfer

Embryo transfers were performed on two different days for each embryo transfer method. In frozen embryo transfer, there were 36 transfers on the third day with 12 successes, resulting in a clinical pregnancy success rate of 33.33%. On the fifth day, there were 258 frozen embryo transfers with 140 successes, resulting in a clinical pregnancy success rate of 54.26%. In fresh embryo transfer, there were 29 transfers on the third day with 12 successes, resulting in a clinical pregnancy success rate of 41.38%. On the fifth day, there were 67 fresh embryo transfers with 31 successes, resulting in a clinical pregnancy success rate of 46.27%. The clinical pregnancy success data for both embryo transfer methods were compared according to the transfer day category. Each transfer day category had a similar difference in success rate range. On the third day of embryo transfer, there was a difference of 8.05% with a higher success rate in fresh embryo transfer, while on the fifth day, there was a difference of 7.99% with a higher success rate in frozen embryo transfer. In summary, it was found that embryo transfer on the fifth day had a higher clinical pregnancy success rate compared to the third day in both embryo transfer methods (Figure 2).

c. Clinical pregnancy rate based on maternal age

The clinical pregnancy success rates based on the maternal age range for both embryo transfer methods were also compared. The age range 25-29 years had a difference of 20% with predominance of frozen embryo transfer, age range 30-34 years with a difference of 5.23% with predominance of fresh embryo transfer, age range 35-39 with a difference of 14.29% with predomincance of frozen

embryo transfer, age range 40-44 years with a difference of 25.98% with predominance of frozen embryo transfer, and the age range 45-49 years with a difference of 20% with predominance of frozen embryo transfer. Overall, frozen embryo transfer significantly outperformed fresh embryo transfer in every age range except for the 30-34 years age group. However, when compared to the differences in each age range, the difference in the 30-34 years age range is the least significant (Figure 3).

d. Clinical pregnancy rate based on duration of infertility

The clinical pregnancy success rates based on the duration of years of infertility for both embryo transfer methods were compared. The 1-5 years duration had a difference of 1.72% with predominance of frozen embryo transfer, 6-10 years with a difference of 8% with predominance of frozen embryo transfer, 11-15 years with a difference of 27.9% with predominance of frozen embryo transfer, and 16-20 years duration with no difference because there were no clinical pregnancy successes in both embryo transfer methods. Overall, frozen embryo transfer performed better in every duration category of years of infertility except for the 16-20 years duration, where there was no clinical pregnancy success in either embryo transfer method (Figure 4).

e. Clinical pregnancy rate based on IVF indication

The clinical pregnancy success rates based on the indications for IVF were compared. Female indications had a difference of 9.77% with predominance of frozen embryo transfer, male indications with a difference of 0.15% with a slight predominance of fresh embryo transfer, male and female indications with a difference of 6.5% with predominance of fresh embryo transfer and unexplained with a difference of 19.34% with a significant predominance of frozen embryo transfer (Figure 5).

f. Clinical pregnancy rate based on endometrial thickness

The clinical pregnancy success rates based on the thickness of the endometrial lining in both embryo transfer methods were compared. A thickness of 6-7.9 mm had a difference of 10%, a thickness of 8-9.9 mm had a difference of 13.82%, a thickness of 10-11.9 mm had a difference of 14.91%, and a thickness $\geqslant$12 mm had a difference of 4.36%. Overall, the clinical pregnancy success rate for endometrial lining thickness $\geqslant$12 mm was not significantly different between the two embryo transfer methods (Figure 6).

Discussion

The results obtained were in line with the research conducted by Ku et al. (2012), which showed a difference in the clinical pregnancy success rate of 6.8% (P=0.376). Therefore, it can be concluded that there is no significant difference between the two embryo transfer methods. Similarly, a study by the Massachusetts Medical Society in 2018 on women with polycystic ovarian syndrome found a non-significant difference in the clinical pregnancy success rate of 2.5%.

These non-significant results can be influenced by the significant difference in sample sizes between the two embryo transfer methods, with a larger sample size for frozen embryo transfer, as this method has become more common. Additionally, many factors can play a role in the success or failure of clinical pregnancy in both embryo transfer methods (Ku et al., 2012). These factors are further divided into various

categories, making the samples highly heterogeneous, and many aspects can affect the outcomes. This becomes problematic because of the heterogeneity among subjects in terms of age, day of transfer, duration of infertility, indications for IVF, and other factors. When a population is highly heterogeneous, a larger sample size is needed to reflect the population's diversity (Susanti, 2005) and make the results more robust (Evans et al., 2014).

The diversity in maternal age is one of the factors that can affect clinical pregnancy success in this study. Based on the data obtained for frozen embryo transfer, it was found that the number of procedures in women aged ⩾35 years was higher than in those aged ⩽34 years. Women aged ⩾35 are categorized as advanced maternal age (McCall, Nair, and Knight, 2017) and are associated with decreased ovarian reserve and oocyte competency (Ubaldi et al., 2019), which can reduce the clinical pregnancy success rate in IVF. This is consistent with the results obtained in this study. Therefore, the predominance of advanced maternal age (AMA) with a lower success rate in frozen embryo transfer in this study can reduce the difference in outcomes between the two methods.

Furthermore, it was found that one of the indications for IVF in both embryo transfer methods was unexplained. This indication had the largest number of cases in the frozen embryo transfer group. This makes it difficult to further describe the pregnancies and failures that occurred, reducing the certainty of the comparison. In other words, the unexplained indication can also lower the clinical pregnancy success rate in frozen embryo transfer, making the difference in outcomes between the two methods non-significant.

The characteristics of the endometrium can also influence clinical pregnancy success. In addition to endometrial wall thickness, the triple-line pattern on the endometrial wall plays a role in reflecting endometrial proliferation. The presence of the triple-line pattern on the day of hCG insertion is associated with a higher pregnancy rate compared to its absence. When associated with endometrial wall thickness, patients with endometrial wall thickness >8 mm and a triple-line pattern have a significantly increased clinical pregnancy success rate (Yang et al., 2018). The absence of the triple-line pattern can indicate premature secretory changes in the endometrium and signal that the window of endometrial receptivity has passed (Bourgein and Devroey, 2003). Similar results in both embryo transfer methods can be influenced by this factor. There is a possibility that patients undergoing fresh embryo transfer have a higher total number of triple-line patterns, while patients undergoing frozen embryo transfer have a lower total number of triple-line patterns, thereby reducing the clinical pregnancy success rate. However, this would need to be confirmed with complete data on the presence of triple-line patterns in patients for further research.

Hormone levels also play a role in the success of clinical pregnancy, including progesterone and hCG levels. In the context of IVF, an early or premature increase in progesterone levels can influence pregnancy success. Premature progesterone increase is defined as an increase in serum progesterone concentration towards the end of the luteal phase. Previous research has shown that this leads to significantly lower implantation and pregnancy rates in embryo transfer (Bosch et al., 2003). This is also supported by a similar study by Mahatma Gandhi Medical College and Hospital, which stated that this condition can lead to lower clinical pregnancy success rates (Ashmita, Vikas, and Swati, 2019). Therefore, the similar results in both embryo transfer methods could also be caused by this factor. There is a possibility that patients undergoing fresh embryo transfer have a lower premature progesterone increase, while patients undergoing frozen embryo transfer have a higher premature progesterone increase, thereby reducing the clinical pregnancy success rate. However, this would also need to be confirmed with complete data on hormone levels in patients for further research.

In the research process, there are several limitations encountered that should be taken into consideration

for future similar research. Some of these limitations include:

1. There is a significant imbalance in the sample size between the two methods, with a small sample size for fresh embryo transfers, which may not accurately reflect the true clinical pregnancy success.
2. Lack of data related to the detection of clinical pregnancy in patients, including the gestational age at examination and specific detection methods used.
3. Insufficient data regarding endometrial lining patterns, the number of IVF cycles undergone, and other patient health histories.

Conclusions

The difference in clinical pregnancy success between the two embryo transfer methods is 6.91% with a p-value of 0.176, which is considered to indicate no significant difference in the clinical pregnancy success rate between fresh embryo transfer and frozen embryo transfer to determine which method is superior.

Declarations

Ethics
All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee. This study was conducted after the approval of Universitas Airlangga research ethics committee.

Consent for publication
Not applicable.
Availability of data and materials
Please contact the author for data requests.

Competing interest
The authors declare that they have competing interests.

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Authors' contributions
AA,ZF — study conception; IRSI — data collection; AA—data acquisition, data analysis, manuscript drafting; ZF,BS,SD—critical revision, final manuscript approval.

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