Effect of Echogenic Catheter Usage During Embryo Transfer on Implantation in the in vitro Fertilization Program

Ida Bagus Putra Adnyana, I Gusti Ngurah Wiranta Permadi, and Nicholas Renata Lazarosony

ABSTRACT

Background: In vitro fertilization is the final option for treating infertile couples. The main determinants of the success of an in vitro fertilization (IVF) program are embryo quality, endometrial receptivity, and embryo transfer technique. When performing an embryo transfer, try to use a soft catheter and easily visible in the uterus with ultrasoundography (USG) monitoring. One solution to this is soft echogenic catheter, as the echogenicity is shown and seen with USG will be able to reduce trauma and excessive uterine manipulation, and increase embryo implantation in the uterine wall.

Objective: To determine the effectiveness of echogenic catheter during embryo transfer in increasing implantation success.

Materials and Methods: This study was a clinical trial conducted at the IVF unit at Bali Royal Hospital Denpasar from August 2018 to December 2019. All participants who took part in the IFV program, who met the requirements, were split into two groups. The case group was echogenic catheter group and the non-echogenic/standard catheter group, which served as the control group. The outcomes of both groups were then identified and compared. The results of this study were statistically tested using SPSS 13 method.

Results: For this study, 38 samples were collected and split into two groups. Each case and control groups had 19 samples. There was no significant difference between two groups of all the confounding variables, except for the antral follicle with a mean of 5.58 ± 2.219 in the echogenic catheter group compared to 7.58 ± 2.893 in the non-echogenic catheter group. While the implantation outcome was 3 times greater in the echogenic catheter group, with 6 (31.6%) samples compared to 2 (10.5%) samples in the non-echogenic catheter group, the difference was not statistically significant (p > 0.05).

Conclusion: There is no significant difference between the outcome of echogenic catheter group and non-echogenic catheter group.

Keywords: Echogenic catheter, embryo transfer, implantation, non-echogenic catheter.

I. INTRODUCTION

Many married couples in Indonesia, including Bali, still struggle with infertility. Infertility is defined as failure to have another pregnancy after more than a year of having sex regularly and not using contraceptive method (secondary infertility). According to BPS data, it is estimated that 12% of married couples are unable to have children. In vitro fertilization (IVF) is known as the final option in the treatment of infertility. This method is performed to increase the chances of pregnancy in infertile couples who have tried and failed other infertility treatments [1], [2].

There are several things that must be considered in order to improve the success of embryo transfer. The first and most important step is to avoid uterine contractions. The second step is to assess uterine cavity and utero-cervical angulation. Among the techniques that can improve the efficiency of embryo transfer are the use of an ultrasound monitor, the type of catheter, the implantation of embryo in uterine cavity, and so on. Systematic reviews and meta-analysis were conducted, evaluating catheter hardness as single variable in relation to successful embryo transfer. When compared to a hard catheter, the use of soft embryo catheter resulted in a significantly higher pregnancy rate [3], [4].

The mechanism of ultrasound during embryo transfer which improves clinical pregnancy and implantation remains unclear, though the most favorable factor is confirmation of a clearly visible catheter tip in uterus. Some studies have suggested that using ultrasound during embryo transfer improves IVF outcomes due to easier transfer, avoiding bleeding, and/or repeated transfer, or by placing embryo in the middle of the uterine cavity [5], [6].
II. MATERIALS AND METHODS

This study is a randomized, single-blind controlled clinical trial that compares the effectiveness of echogenic catheter usage and standard catheter in an attempt to improve IVF outcome (implantation rate), as well as the ease and length of time required to perform an embryo transfer. This research was conducted from August 2018 to December 2019 at the IVF unit at Bali Royal Hospital Denpasar. There were 38 samples, with case group (echogenic catheter) and control group (non-echogenic/standard catheter) each had 19 samples.

The population and samples of the study were infertile couples who managed to complete IVF program at Bali Royal Hospital Denpasar, after being selected by a doctor or IVF team at Bali Royal Hospital Denpasar.

Samples were taken by randomizing blocks using computer, which the samples were divided into two groups (case and control group). Data and standard deviation were analyzed with SPSS 13. Chi-square test and Fisher’s exact test were used to compare qualitative variables, and Student’s t-test was used to compare quantitative data. The p value < 0.05 and CI 95% indicates that this study is significant.

III. RESULTS

According to Table I, more participants were under 35 years old, while most common cause of infertility of both groups was tubal factor. Duration of infertility was nearly identical between echogenic catheter group and standard catheter group. Baseline FSH was examined during day 2-4 of menstruation, the majority had FSH levels between 3-20 IU/l, with 19 samples were in the echogenic group and 17 samples were in the non-echogenic group. In terms of antral follicle count, in the echogenic catheter group, 12 samples had <6 antral follicles, whereas more of the non-echogenic group (13 samples) had >6 antral follicles.

The characteristics of ovarian stimulation, ovum pick up, and IVF outcomes in both groups are shown in Table II. Long-protocol ovarian stimulation method is more common than short-protocol. In the echogenic catheter group, 16 samples were on long-protocol method and 3 samples were on short-protocol. While in the non-echogenic catheter group consisted 13 samples with the long protocol and 6 samples with the short protocol. The average total dose of FSH was <30 ampules on 14 samples of echogenic catheter group and 12 samples in the non-echogenic catheter group. Average LH dose used was 2-15 mIU/mL, with 11 samples for echogenic catheter group and 8 samples for standard catheter group. Follicle count obtained during HCG injection was divided into two groups (<6 and >6 follicles).

The results showed that when there were <6 follicles, there were 12 samples in the echogenic group and 14 samples in the non-echogenic group. Estradiol level was also measured during HCG injection. Both groups had more samples with estradiol level less than 3000 pg/ml, with 16 samples each from echogenic and non-echogenic group. Meanwhile, in terms of the number of embryos transferred, it was found that <3 embryos were more common than >3 embryos. There were more bad embryo score in the standard catheter group than good embryo score. In contrast to the characteristics of other variables, all samples showed good criteria for endometrial receptivity.

Table III shows the characteristics of embryo transfer in both study groups. The distance between catheter tip and uterine fundus was measured. Most samples were measured at a distance of 1-2 cm between the catheter tip and uterine fundus. 16 samples were in the echogenic catheter group.
and 13 samples were in the standard catheter group. There was one sample in the standard catheter group that the distance was not clearly visible. Meanwhile, based on catheter visualization, mostly had good visualization, with 15 samples from echogenic catheter group and 13 samples from standard catheter group. Ease of transfer was found easier on 10 samples from echogenic catheter group and 9 samples from standard catheter group. Other 6 samples from each group were hardly transferred. Most samples were transferred with the duration of 0.5–1 minute.

According to Table IV, it was discovered that 6 samples in the echogenic catheter group and 2 samples in the standard group had implantation. This suggest that the incidence of implantation in the echogenic catheter group is three times greater than the standard catheter group.

TABLE IV: IMPLANTATION RATE AND PREGNANCY OF BOTH GROUPS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Echogenic catheter (n=19)</th>
<th>Standard Catheter (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical pregnancy</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Analysis was done on most of the variables of both groups, namely echogenic catheter group and standard catheter group. It was found that there was an average difference, except for antral follicle which was significantly difference between the two groups (p < 0.05).

The primary analytical test of this study was to compare the success of implantation in embryo transfer using an echogenic catheter. From 38 samples, 19 samples were in the echogenic catheter group and 19 samples were in the standard catheter group. Overall success of implantation was on 8 samples from 38 samples. The echogenic catheter group had 6 of 19 (31.6%) samples implanted and the standard catheter group had 2 of 19 (10.5%) samples implanted. This suggests that using an echogenic catheter has a threefold success rate as compared to implantation with a standard catheter. However, the chi-square statistical test revealed no significant difference between the two groups (p >0.005). Other confounding variables, such as maternal age, duration of infertility, type of infertility, basal hormone levels (FSH, E2, LH, Prolactin), antral follicle, preovulatory E2 levels, etc. There was no significant difference in the occurrence of pregnancy between two groups.

IV. DISCUSSION

Clinical trials have been conducted to determine the effectiveness of the echogenic catheter to improve the success of implantation in the IFV program, with the following results.

Samples’ characteristics such as maternal age is believed to impact pregnancy success in various studies, which is associated with decreased ovarian reserve, as well as antral follicles, basal FSH, LH, and E2 hormones, which are used to predict ovarian reserves. The likelihood of ovulation and pregnancy decreases with age, however it turns out that other ovarian reserve tests are still required because age factor alone is not particularly accurate in predicting results. Reference [7] developed a mathematical model to calculated the reduction in follicle number with increasing age. Fig. 1 illustrates a simulation of the mathematical model’s calculation. The figure shows that the number of primordial follicles at birth is roughly 700,000 follicles (point A), and declines to 1,000 follicles during menopause (point C) [7].

The mean maternal age in this study was 33.53 ± 4.6111 years old for the echogenic catheter group and 32.95 ± 5.768 years old for the non-echogenic catheter group. There was no significant difference between two groups. According to a demographic study, fertility peaks at the age of 20 and decrease at the age of 30 [7].

Similarly, basal hormone levels such as FSH, LH, and E2 are predictors of ovarian reserve. In a study, no pregnancy was detected on basal FSH levels greater than 20 mIU/ml. In the natural cycle, subfertile women with high FSH levels have worst follicle growth compared to normal FSH levels [8].

The mean estradiol level obtained in this study was 37.93 ± 16.21 pg/ml in the echogenic catheter group and 42.82 ± 23.23 pg/ml in the non-echogenic catheter group, however there was no statistically significant difference between the two groups. Reference [9] conducted a retrospective study of the association between basal estradiol levels and cycle cancellation rate in the IVF program of 2624 women. They concluded that basal E2 levels of <20 pg/ml or >80 pg/ml had a high risk of cancelling the IVF cycle. In another study, it was stated that successful ovulation was associated with basal estradiol levels but not associated with pregnancy outcome. Basal estradiol levels will become more predictable in patients with advanced reproductive age, especially when paired with basal FSH levels. No information has been studied regarding the basal estradiol level utilized in the general subfertile population. Before further review, more research on basal estradiol in spontaneous cycles is required [10].

In our characteristics study, antral follicles had a mean of 5.58 ± 2.219 in the echogenic group and 7.58 ± 2.893 in the non-echogenic group. It was determined to be statistically significant with p = 0.023 (p < 0.005). Several research have been conducted to investigate the association between antral follicle count (AFC) and ovarian reserve. The premise is that the number of antral follicles derived from a developing follicle cohort coincides with the number of primordial follicles or ovarian reserve. AFC is defined as the number of follicles with a diameter of <10 mm which can be detected by ultrasound examination in the early follicular phase. Overall, the findings of this study suggest that AFC examination is more promising as a method to evaluate ovarian reserve [11]-[13].
Fig. 2. Relationship between number of antral follicles obtained in the early follicular phase and chronological age.

Other variables were compared between the two groups, such as duration of infertility, type of infertility, dose of FSH and LH, duration of embryo transfer, catheter visualization, ease of transfer, distance from catheter tip to uterine fundus, etc. In this study, there are no significant difference of the variables. Indeed, when compared between the two groups, especially catheter visualization, ease of transfer, and duration of transfer in several studies, there were differences between the use of echogenic catheter and standard catheter.

Reference [14] discovered that the time interval from inserting catheter to placing the embryo in the uterine cavity is an important factor in the success of implantation and pregnancy.

In fact, the shorter time needed to manipulate embryo during embryo transfer may increase the number of pregnancy in the IVF program [5], [6]. Another study suggests the duration of embryo transfer from the time the clinician holds the catheter to release embryo is significantly shorter in the echogenic catheter group than in the standard catheter group [15].

In this study, we aimed to compare the outcome of IFV in embryo transfer using catheter, which was compared between echogenic catheter as case group and standard (non-echogenic) catheter as control group. Each group had 19 samples. Overall success of implantation was on 8 samples from 38 samples. The echogenic catheter group had 6 of 19 (31.6%) samples implanted and the standard catheter group had 2 of 19 (10.5%) samples implanted. This suggests that using an echogenic catheter has a threefold success rate as compared to implantation with a standard catheter. However, the chi-square statistical test revealed no significant difference between the two groups (p > 0.005).

There are several possibilities that could explain why this study is not significant. First, the number of samples was insufficient because, at the time of sample calculation, based on the assumption that the success of implantation increases from 20% to 50%, while the success rate in this study was only 31.6%. Second, dr. Jacqueline, who reviewed the success of IFV at Sanglah Hospital, Denpasar stated in her research that the decrease success of IFV could be attributed to poor instruments used during embryo culture, such as the absence of temperature monitoring (warming dish) during oocyte examination, and setting the pH of the buffer media, which would interfere with oocyte and embryo development. Table V shows how to test or monitor laboratory or media to ensure successful embryo culture.

V. CONCLUSION

The results of this study showed that there was a significant difference between the two groups in the antral follicles. According to main analysis’ findings, implantation success was 3 times greater in the case group compared to control group, but the was no statistically significant difference.

TABLE V: SYSTEM VALIDITY TEST AT IVF LABORATORY

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Test</th>
<th>Frequency of Testing</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO2 Incubator</td>
<td>CO2</td>
<td>Weekly/ Daily/ As required</td>
<td>Fryte Gauge/ Thermometer/ Mouse biosassay</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>Temperature</td>
<td>Daily/ Monthly/ Every use</td>
<td>Max/m in term/ Surface term/ Strip term</td>
</tr>
<tr>
<td>Heated Stages</td>
<td>Temperature</td>
<td>Monthly/ Monthly/ Every use</td>
<td>Max/m in term/ Surface term/ Strip term</td>
</tr>
<tr>
<td>Hot blocks Incubator</td>
<td>Temperature</td>
<td>Monthly/ Every use</td>
<td>Max/m in term/ Surface term/ Strip term</td>
</tr>
<tr>
<td>Cryopreservation equipment</td>
<td>Function</td>
<td>Every run/ Test run</td>
<td>Max/m in term/ Surface term/ Strip term</td>
</tr>
</tbody>
</table>

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DOI: http://dx.doi.org/10.24018/ejmed.2022.4.5.1475

Vol 4 | Issue 5 | October 2022
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