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RESEARCH

Factors Related to the Success of IVF Program in Morula BMC Clinic Padang

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Abstract

Introduction*: Infertility is the failure of a couple to get pregnant 12 months after having regular sex without contraception. One in seven couples even have to be treated using Assisted Reproductive Technology (TRB). The most widely used TRB is In Vitro Fertilization (IVF). In general, the success rate is in the range of 40-50%. In Indonesia, there are 32 clinics providing IVF program with a success rate of 30-40%. The success rate of IVF is influenced by multi variables that affect directly or indirectly including age, Antral Follicle Count (AFC), Anti Mullerian Hormone (AMH), basal Follicle Stimulating Hormone (FSH), number of egg cells, egg quality, sperm quality, embryo quality, and endometrial thickness.*

Objectives: *This study aims to determine the factors associated with the success of IVF program*

Methods: *This study used a cross-sectional analytic study design which was conducted on 77 medical records of patients undergoing IVF program at Morula Clinic BMC Padang from January 2018-December 2020. All data were then analyzed using univariate, bivariate and multivariate analysis with appropriate statistical test;*

Results: *The average age of the study subjects was (33.4 ± 3.93) years, the average length of infertility was (6.73 ± 3.69) years, the most used antagonist protocols (88.16%), with the most common causes of infertility being factors sperm (48.9%) and overweight BMI (36.4%). From the bivariate analysis, it was found that the factors related to the number of eggs were age (r = -0.349), AFC (r = 0.471), FSH (p 0.02), and AMH (p < 0.01) with the dominant factor being AMH. Egg quality was related to AFC (p 0.007) and FSH (p 0.002), with the dominant factor being AFC. Embryo quality correlated with egg quality (p < 0.01). Meanwhile, the success of implantation was dominantly related to the embryo quality factor (0.034);*

Conclusion: *The most dominant factor to the success of IVF program is the quality of the embryo.*

Keywords*: IVF, IVF success.*

INTRODUCTION

Infertility is the failure of a couple to get pregnant 12 months after having sexual intercourse regularly (2-3x a week) without contraception. Primary infertility is the inability of a woman to conceive and maintain a pregnancy or give birth to a live child while secondary infertility is the inability of a woman to have children or to maintain her pregnancy in women who have been pregnant or have given birth to live children.[1,2]

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According to WHO, 60-80 million couples in the world have difficulty having children. According to the 2015 National Socio-Economic Survey (SUSENAS) there were 48,609,000 couples of childbearing age (EFA) in Indonesia and 729,428 EFA in West Sumatra with an estimated 10–15% difficulty in getting offspring due to various reasons. 2-10% of couples experience failure to have children naturally, and one in seven married couples come to a specialist for consultation and even have to be treated using Assisted Reproductive Technology (ART).[3,4]

Advances in assisted reproductive technology for infertile couples have developed rapidly since 1976. In general, the IVF success rate is in the range of 40-50%. Indonesia has 32 IVF service providers with a success rate of 30-40%. According to the Indonesian In Vitro Fertilization Association (PERFITRI), IVF services in Indonesia are increasing by an average of 65% every year. West Sumatra has one clinic providing IVF services, namely the Morula BMC Clinic with 142 cycles of IVF for the last 3 years.[3.5]

As the number of follicles decreases, oocyte quality also decreases, mainly due to increased meiotic nondisjunction, resulting in an increased rate of oocyte and embryo aneuploidy in elderly women. The increasing incidence of aneuploidy also causes an increase in the abortion rate in older women.1 The study of Spanderfer et al found that after the age of 35 years, the implantation rate decreased by 2.77% per year.[6] Another study conducted by Van koooij et al showed that there was a 20% decrease in implantation rates after 37 years of age.[1,7]

Antral Follicle Count (AFC) is one of the modalities for estimating ovarian reserve.[8] FAccording to the study, the IVF cycle cancellation rate was significantly higher in patients with increased FSH day 3, due to a low ovarian response and thus not undergoing the embryo transfer (ET) procedure.[9] After age 40, both implantation and clinical pregnancy rates are lower in patients with elevated basal FSH.[10]

The relationship between oocyte quality, embryonic development, and IVF outcome has been extensively studied. Assessment of oocyte quality can be assessed from the morphology of the oocyte, namely the structure of the perivitelline space (PVS), the zona pellucida (ZP), and the morphology of the polar body (PB). Research shows oocytes with good quality, morula stage embryos, have 8 cell embryos, less fragmentation and better embryo rates significantly increase implantation success and pregnancy.

Oocyte fertilization can be done by conventional means or bytechnique Intracytoplasmic Sperm Injection (ICSI). The use of conventional techniques has begun to be abandoned and replaced by ICSI techniques (80.8%).[11] This specific period, known as the window of implantation(windowof implantation/ WOI), opened five days after the action of endogenous or exogenous progesterone and closed two days.[12] Endometrial receptivity can be assessed by ultrasound by measuring endometrial thickness and triple line imaging.[13] The relationship between endometrial thickness and implantation rate in several studies has shown that an endometrial thickness of < 8 mm is associated with decreased implantation rates and the degree of periendometrial vascularization (Doppler) is associated with

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endometrial receptivity.[14] On going pregancy is defined as a pregnancy that has reached gestational age 20 weeks.[15] Meanwhile, the Take home baby rate is the number of couples carrying at least 1 healthy baby as a result of IVF divided by all couples who underwent embryo transfer.[16]

METHODS

This type of research is analytic with a cross-sectional analytic study design. The research was carried out from May 2021 - August. The research data was obtained by taking secondary data from the medical records of patients undergoing IVF program at the Morula BMC Padang clinic during the period January 2018 - December 2020.

The population of this study were all patients who underwent IVF program at the Morula IVF clinic BMC Padang for the period January 2018 - December 2020. The research sample selected was part of the study population that met the criteria with a simple random sampling technique, which was 77 people. Subject inclusion criteria were patients who underwent IVF program for the first time and patients who underwent repeat IVF program.

The data were statistically analyzed which was assessed using a computerized system, namely univariate, bivariate and multivariate analysis. Univariate analysis was conducted to see the frequency distribution of each independent variable and dependent variable. Bivariate analysis was carried out using t-test or chi-square and it was said that there was a significant relationship if the p value <0.05 was obtained. Multivariate analysis to assess what factors most influence the success of IVF program. This research has passed the ethical review with letter number 77/KEPK/2021

RESULTS

This study was conducted from May 2020 - August 2021 by examining the medical records of IVF program patients at BMC Padang Morula IVF clinic in January 2018 - December 2020, obtained by 77 respondents. The characteristics of the most respondents have an overweight BMI of 28 (36.4%) respondents, the average length of infertility is 6.73 ± 3.69 years, Most of patient (89.6%) are first time doing IVF, the most common cause of infertility is sperm factor which is 67 (48.9%) respondents.

There is a negative correlation between age and the number of eggs with coefiisen relation (r) = -0.349 with a low degree of correlation. There was no significant relationship between age and egg quality, but the age group of respondents 20-35 years old had the most good egg quality of 58.1%. There is also no significant relationship between age and embryo quality, but good embryo quality is more widely obtained in the age group of 20-35 years and >35-40 years compared to the age of > 40 years. There is a positive correlation between AFC and the number of eggs with a relation coefficient (r) = 0.471 with a moderate correlation rate. There is a significant relationship between AFC and the number of eggs.

The average number of eggs was obtained in the high AMH group of 16.93 ± 5.86. There

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is a negative correlation between FSH and the number of eggs with a relation coefficient (r) = -0.272 with a low degree of correlation. There is a meaningful relationship between AFC and egg quality ($p<0.05$). The normo responder group had the most good egg quality at 58.6%. There is a positive correlation between the number of eggs and the number of embryos with a coefficient of relation (r) = 0.687 with a strong correlation rate.

There is a significant relationship between egg quality and embryo quality. The quality of good embryos is obtained in the quality of Good eggs, which is 42 (89.4%). There is no significant relationship between sperm quality and embryo quality, and relationship between total embryos transferred and implantation. There is a significant relationship between embryo quality and implantation. Pregnancy occurs most in the quality of good embryos, which is 54.1%.

The dominant factor associated with total egg cells is AMH. Dominant factor associated with egg quality is AFC. The quality of the dominant egg is related to the quality of the embryo ($p<0.05$). The dominant factor associated with implantation success is the quality of the embryo ($p<0.05$).

DISCUSSION

The study was conducted on 77 respondents who conducted a IVF program at Morula Padang Clinic from January 2018 to December 2020. The age of the most respondents in the age group < 35 years, most had an overweight BMI (36.4%) with an average infertility period of 6.73 ± 3.69 years, most new to IVF for the first time (89.6%), the most widely used protocol is antagonistic with triger ovidrel, and the cause of infertility is the most commonly male factor, sperm disorder is 67 (48.9%).

From the study, the total egg cells obtained at the time of OPU are meaningfully related to age, AFC, FSH and AMH. Amh is the dominant factor associated with total eggs. The results of this study align with the theory that maternal age and ovarian reserve are factors that determine the success of IVF. Age increases lead to a decrease in total ovarian reserve from 1-2 million at birth, to 300,000-400,000 at puberty and shrinks to only 25,000 by age 40. Razi et al(2018) research in Iran also found a meaningful association between age and decreased egg total. Ovarian reserve can be measured by calculating AFC, basal FSH levels and AMH. The Halte et al (2011) study in Sweden showed a strong association between ovarian reserve, measured by AFC and IVF success. The pregnancy rate increased from 15% to 25% with an increase from 5 to 11 antral follicles. The advantage of AFC is that it can be measured easily in the clinic, quickly, but the disadvantage is the lack of standardization in ultrasound equipment, techniques, and standard antral follicle size. Steinberg et al(2018) study in Chicago states AMH can also be used to assess total oocytes rather than oocyte quality. Increased AMH levels will increase the total oocytes obtained at the time of OPU. The Riggs et al study (2008) in Virginia, USA also states that AMH values have the best correlation with total oocytes at the time of OPU versus FSH.[24] Jefreyy et al study (2005) in New York showed that oocyte yields were significantly lower in patients with elevated basal FSH levels. [10]

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According to the theory that when total ovarian reserve is reduced, the quality of the egg also decreases, mainly due to increased nondisjunction of meiosis, resulting in an increase in chromosomal abnormalities in the egg and embryos especially in elderly women.1 The quality of the egg in this study was found to be significantly related to AFC and FSH, with AFC being the dominant factor. Research by EB Johnstone (2010) in California San Francisco showed a decrease in the AFC percentile in women with infertility, suggesting that AFCs may be markers of total and oocyte quality. Another study by Abdalla et al (2004) in London England also stated that increased basal FSH levels were associated with low ovarian reserve (decrease in total oocytes) and poor oocyte quality. But in this study there was no meaningful relationship between age and AMH with egg quality. This difference in results can be caused by several factors, including: the sample used distribution is uneven between age groups, the assessment of egg quality is not clearly written on the medical record, so there is a possibility of differences in perception between examiners and researchers and limitations of sampling in only one place. These results were also found in a Study steinberg et al (2018) in Chicago that said increased AMH levels are an indication of higher ovarian reserve. This applies to egg quantity, but not always true to egg quality because patients with high AMH levels are shown to have embryos that develop into blastocysts at lower levels than controls. [23]

The success of IVF requires quality embryos. Age, egg quality and sperm quality will affect the quality of the embryo. [4] In this study, the quality of embryos obtained is predominantly related to the quality of the egg. The quality of embryos in the study was measured by a combination of cumulative effects of the six oocyte parameters (morphology, size, cytoplasm, ZP structure, PVS, and first PB morphology). Research Larazoni et al (2015) in New York states that better oocytes improve total and better embryo quality. The age and quality of sperm obtained was not related to the quality of the embryos in the study. This is in accordance with research Razi et al (2014) in Iran which states that age is indeed a predictor for embryo quality. This correlation of age and embryo quality is associated primarily with the quality of oocytes which are the main determinants of embryonic development in women. But embryos that morphologically look normal (of good quality) can have abnormal chromosomes, which will eventually result in low pregnancy rates. The results of this study are due to the characteristics of the study subjects who have the most cause of infertility, namely sperm factors, where sperm quality is mostly abnormal (89.6%) but all fertilization is done by ICSI.

The success of implantation is determined by the total embryo and the quality of the embryo transferred as well as endometrial receptiveivity. But in this study the quality of embryos was the dominant factor associated with implantation, while total embryonic and endometrial thickness were not meaningfully related to implantation. Kirillova et al's research (2012-2016) in Russia showed all low-quality embryos had lower levels of implantation, biochemistry and clinical pregnancy. Another study conducted by Wintner et

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al (2017) in Israel also found that clinical pregnancy and live birth rate per transfer, were twice as high as the transfer of one good-quality embryo compared to poor-quality embryo transfer. [19] Single transfer embryos were more successfully transplanted compared to the transfer of 2 embryos. This is because the transfer of 1 embryo is usually done if the embryo transfer at the blastocyst stage (good quality embryo). This is in accordance with the research obtained Total embryos transferred are not associated with successful implantation. The Pandian et al (2005) study in Egypt said single embryo transfer significantly reduced the risk of multiple pregnancies, but also reduced the chances of a live birth on an IVF cycle. A potential advantage of elective single embryo transfer is the opportunity to freeze the excess embryo and use it in subsequent cycles. [27] Meanwhile for endometrial receptiveivity in this study was determined by measuring endometrial thickness. Nine studies showed endometrial thickness ≤ 8 mm showed a low degree of implantation. Another study by Sarvi et al (2017) in Iran showed lower pregnancy rates in patients with endometrial thickness of less than 7 mm compared to patients with endometrial thickness of more than 7 mm. 18 However this is not proven in this study, this is due to the weakness of this study, namely in Frozen embryo transfer data endometrial thickness taken at the time of stimulation, not at the time of embryo transfer, and total respondents with embryo thickness ≤ 8 mm slightly

CONCLUSIONS

From the results of this research, it can be concluded that the characteristics of couples undergoing the IVF program are in the age range of 33.4 ± 3.93 years with a length of infertility of 6.73 ± 3.69 years, BMI normoweight, primary infertility, the first time undergoing IVF, using antagonistic protocols, the most common infertility factors are male factors (sperm abnormalities).

There is a meaningful relationship between age and total egg at OPU, antral follicle count (AFC) and total egg at OPU, anti mullerian hormone (AMH) and total egg at OPU, basal FSH with total egg at OPU, antral follicle count (AFC) with egg quality, antral follicle count (AFC) with total egg count (AFC) egg at the time of OPU, Anti Mullerian Hormone (AMH) with Total egg at OPU, basal FSH with Total egg at OPU, antral follicle count (AFC) with egg quality, total egg cell relationship performed by ICSI with total embryo obtained, between egg quality with embryo quality, embryo quality with implantation, the quality of implantation, and the quality of the embryo with implantation.

There was no meaningful relationship between age and egg quality, age with embryo quality, Anti Mullerian Hormone (AMH) with egg quality, sperm quality with embryo quality, Total embryo transferred by implantation, endometrial thickness with implantation.

The dominant factor associated with total egg cells is AMH, the dominant factor associated with egg quality is AFC. The dominant factor associated with the quality of the embryo is the quality of the egg. The dominant factor associated with the success of IVF is the quality of the embryo.

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