

Association of Patient Characteristics with in Vitro Fertilization (IVF) Failure in Graha Amerta Fertility Clinic Dr. Soetomo General Hospital, Surabaya

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Abstract

Background : Due to the development of science and technology in the field of medicine, infertility has been solved by the discovery of one of the most sophisticated ART program, known as IVF. Although this procedure has been carried out for more than 40 years, the failure rate is still very high. This problem is considered to be related with the characteristic of the patient undergoing IVF. This study aims to determine the association between patient's multi-characteristics and IVF failure.

Method : This research is an observational analytic research with cross-sectional method. The determination of the research sample uses a total sampling technique by taking all members of the population in accordance with the conditions.

Result : Out of 102 couples undergoing IVF, 37 couples (36,3%) successfully obtained a pregnancy while the 65 other couples (63,7%) failed IVF or has not obtained a pregnancy. The result of the *p* value between IVF failure and maternal age is 0,03, with BMI 0,532, with sperm quality 0,577, with PCOS 0,297, with endometriosis 0,578, and with POR 0,027.

Conclusion : Out of all the studied patient characteristics, only maternal age and POR are associated with IVF failure with the *p* value of 0,03 and 0,027 respectively. BMI, sperm quality, PCOS, and endometriosis do not show a significant correlation with IVF failure.

Keywords : *IVF Failure, Age, BMI, Sperm quality, PCOS, Endometriosis, POR.*

Introduction

The factors that cause infertility can come from both men and women. However, by the development of science and technology in the field of medicine, infertility has been solved by the discovery of the most sophisticated Assisted Reproductive Technology (ART) program, known as In Vitro Fertilization (IVF). In IVF, the fertilized embryo from outside of the uterus is placed

back into the uterus of the infertile woman so that it develops into pregnancy¹. IVF success was first marked by the birth of Louisa Brown in 1978. The success of IVF is growing rapidly where the initial implantation rates that were <5% per embryo replaced were continuously increased to rates >50%². Therefore, until now, IVF has helped many couples who cannot experience their pregnancy naturally.

Although IVF has been carried out for more than 40 years, the failure rate is still very high. This problem is considered to be related with the characteristics of the patient undergoing IVF. Of the 2552 IVF cycles that had been carried out, only 31.2% of the 7213 eggs that were plucked were successful in becoming good embryos so

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that it can be used in IVF. This fact is reinforced by data showing that only 5% of the 7213 eggs successfully become babies, so the success rate is still very low³. IVF is considered to be a failure if it does not lead to pregnancy, which is indicated by the level of Beta HCG in the blood. If the Beta-HCG level exceeds 25 mIU mL, it is stated that pregnancy has occurred, and vice versa.

There are three important stages during IVF that has a great role in determining its success. These first type of factors is known as the internal factor, namely: (1) the ovulation induction; (2) the fertilization; and (3) the Embryo Transfer (ET). Apart from the internal factors, there are also external factors such as patient characteristics that can cause IVF failure. {Formatting Citation} Patient characteristic factors include the age of the female partners. Post-IVF cumulative pregnancy success rate varies with age, where in the 20-24 years age range it is 40% while in the 40-45 years age range it is 20%. Patient with obesity (BMI > 30 kg/m²) has a greater risk of implantation failure than patients with normal BMI (18.5-24.9 kg/m²). For male patients, sperm quality have an influence on the success of fertilization. The presence of endometriosis and a history of other uterine diseases can affect the success rate of embryo implantation, due to changes in secretory components and endometrial thickness⁴. PCOS are also associated with the quality of the oocytes obtained. Furthermore, the existence of Poor Ovarian Reserve (POR) disease has an effect on the least number of oocytes produced. Some studies have also suggested that there is a twofold increased risk of miscarriage in women with thyroid dysfunction⁵.

IVF failure can cause various problems for couples. With the magnitude of the negative impacts that can occur due to the failure of the IVF program, further studies are needed regarding the correlation of patient multi-characteristic with IVF failure at Graha Amerta Fertility Clinic Dr. Soetomo General Hospital so that it can be useful to optimize the pregnancy rate.

Methods

This research is an observational analytic research with cross-sectional method. The samples in this

study were all couples who underwent IVF in Graha Amerta Fertility Clinic Dr. Soetomo General Hospital from July 2018 to July 2019. Using ordinal data from patients' medical record, patient characteristics data on age, BMI, sperm quality, PCOS, endometriosis, POR, and b-hCG levels were obtained and analyzed. A total of 102 couples who underwent IVF were included in this study. There are two groups of patient, which are patient who succeed to obtained pregnancy and those who failed. From age characteristic, the female partners are divided into three groups: 25-35 years; 36-40 years; and >40 years. The BMI were categorized into four group: <18,5 kg/m²; 18,5-24,9 kg/m²; 25-29,9 kg/m²; ≥ 30 kg/m². The sperm quality was determined by the sperm analysis results data. POR was diagnosed by the guidelines from the European Society of Human Reproduction and Embryology (ESHRE), which is if two of the these characteristics are present: (1) Maternal Age >39; (2) a previous POR which is the retrieved oocyte were under 4; and (3) ovarian reserve test result was abnormal (AFC <5-7 follicles) or AMH < 0.5-1.1 ng/mL)⁶. Patients with discontinuation status who had not completed the cycle, canceled cycle and incomplete data were not included in this study. Ethical clearance was granted by the Health Research Ethics Committee Faculty of Medicine, Universitas Airlangga.

The data of samples were not distributed normally, therefore, data normality test is not required. With non-parametric statistical tests, analyses were performed using the Chi-square test and Fisher's Exact Test on SPSS software. Statistical significance were determined if $p < 0,05$ and the strength of the relationship between two variables were showed from the Contingency Coefficient (C).

Results

A total of 214 medical records were obtained and only 102 of them were eligible for this study. 102 couples underwent IVF were observed and only 37 couples (36,3%) succeeded to obtain pregnancy, whereas the other 65 (63,7%) failed. The association of patient characteristics with IVF failure at Graha Amerta Fertility Clinic Dr. Soetomo General Hospital in the 2018-2019 period is shown in table 1 below.

Table I. Characteristics associated with IVF failure

Characteristics	Succeed IVF group (n=37)		Failed IVF group (n=65)		P value
	n	%	n	%	
Age (years)					0,03
25-35	32	86,5%	43	66,2%	
36-40	5	13,5%	13	20%	
>40	0	0%	9	13,8%	
BMI (kg/m ²)					0,556
<18,5	1	2,7%	4	6,2%	
18,5 – 24,9	25	67,6%	36	55,4%	
25 – 29,9	7	18,9%	19	29,2%	
≥ 30	4	10,8%	6	9,2%	
Sperm quality					0,577
normal	10	27%	21	32,3%	
abnormal	27	73%	44	67,7%	
PCOS					0,297
non-PCOS	35	94,6%	64	98,5%	
PCOS	2	5,4%	1	1,5%	
Endometriosis					0,578
non-Endometriosis	34	91,9%	59	90,8%	
Endometriosis	3	8,1%	6	9,2%	
POR					0,027
non-POR	34	91,9%	48	73,8%	
POR	3	8,1%	17	26,2%	

BMI : Body Mass Index; E2 :Estradiol; IVF: In Vitro Fertilization; POR :Poor Ovarian Reserve; PCOS :Polycystic Ovary Syndrome.

Age and POR characteristics shows a *p* value of 0,03 and 0,027 respectively. Both characteristics show a significant association with IVF failure (*p* < 0,05). Characteristics associated with IVF significantly were showed in table II with Contingency Coefficient value (*C*).

Table II. Contingency Coefficient analysis of characteristics with IVF failure

Characteristics	Succeed IVF group (n=37)		Failed IVF group (n=65)		C
	n	%	n	%	
Age (years)					0,254
25-35	32	86,5%	43	66,2%	
36-40	5	13,5%	13	20%	
>40	0	0%	9	13,8%	
POR					0,213
non-POR	34	91,9%	48	73,8%	
POR	3	8,1%	17	26,2%	

C : Contingency Coefficient; POR: Poor Ovarian Reserve.

Discussion

From the previous study, it is reported that only 5% of the 7213 eggs successfully become babies. In line with the high failure rate of IVF cycles in Indonesia, it is important to evaluate the process for a maximum outcome. Although several reports have been conducted worldwide, studies in Indonesia are still very much needed. This article mentioned the association between age, BMI, sperm quality, PCOS, endometriosis, and POR characteristics with IVF failure.

Most of the couple underwent IVF in Graha Amerta Fertility Clinic Dr. Soetomo General Hospital from July 2018 to July 2019 failed to obtain pregnancy. From 102 couples, only 37 (36,3%) succeeded to obtain pregnancy which is categorized as the successful IVF group. Couples that succeed IVF were mostly aged around 25-35 with no reported success among the observed samples at age over 40. From the statistical calculations, age characteristics with IVF failure were associated significantly ($p < 0,05$) with Contingency Coefficient of 0,254. The results described above verify the findings of a previous study in Berlin by Rendtorff et al. in 2016 which presented data from Charite University

Hospital 2004-2014 on the percentage of pregnancies in a group of women: 43.3% for 19-29 years old; 48.8% for 30-39 years old; 5.2% for 40-44 years old; and the smallest percentage of successful pregnancy at 0.34% for women aged over 45 years old⁷. Another study was done by Coughlan et al., which showed similar results that explained the negative effect of age on embryo quality in IVF. This is related to the risk of aneuploidy which increases with age⁸. Dicker et al. also found a lower IVF success rate at women aged over 40 with p value of $<0,05$ ⁹. A different study in 2014 by Hendarto showed that there is a significant difference of oocyte count in a group of age < 35 and ≥ 35 ($p < 0,05$)¹⁰. The association between age and IVF failure is explained by Saphiro et al. in 2016, which explains that the uterus of elderly women has decreased vascularity, endometrium thickness, and prostaglandin production which are related to embryo implantation¹¹.

BMI characteristics were reported to have a negative impact on determining IVF success. Previous study by Comstock et al. showed significant results with p value of 0,007 between BMI and IVF success. Comstock et al. stated that the rate of blastocyst formation in women with normal weight was significantly better than in

obese women¹². This reason leads to the influence of oocyte quality on embryo development in obese women which ultimately predisposes to IVF failure. The result in this study was contradictory with a previous study ($p < 0,556$). The dissimilar results of these studies can be caused by many factors. Various factors during the process of carrying out the procedure such as expert skills and the technology used also have a very important role in determining IVF outcome, which in this study was not examined so that it affects the final result. Another factor that affects IVF outcome is the characteristics of men, one of which is the quality of sperm which is different for each patient.

In order to have a successful IVF and obtain pregnancy, the male partners have a primary role in giving the sperm cell that is going to fertilize the oocyte. In this study, most of the couple that were successful in IVF have normal sperm cells in terms of morphology, motility, and amount. From the statistical calculations, we found insignificant result with p value of 0,577 between sperm quality and IVF failure. This result is contradictory with the previous study that states sperm cells must be able to carry out its function to penetrate zona pellucida in order to fertilize the oocyte¹³. However, men with abnormal sperm characteristic are unable to do that, which leads to IVF failure. Another study by Respati explained that embryo quality is affected by sperm quality and there is a significant correlation between embryo quality and IVF failure¹⁴. This contradictory result is affected by many factors, and it is assumed that the severity of abnormal sperm could affect IVF failure.

We also studied the association of PCOS characteristic with IVF failure. Statistical test was conducted and the results show an insignificant p value of 0,297. This result was not in line with a previous study in China by He et al. in 2019 which stated that PCOS has a negative effect on IVF¹⁵. Similar results were observed in a study conducted by McCormick et al¹⁶. The results showed that there was no statistically significant effect of women with PCOS towards IVF failure. McCormick et al. conducted a study on obese women which are divided into two groups, namely obese women with PCOS and obese women without PCOS¹⁶. The analysis results of the study explained that there was a decrease in the implantation rate in obese women with PCOS, but the end result or pregnancy of IVF in the two groups

showed that there was no significant difference.

The characteristics of endometrium where the implantation will occur have a significant role in determining IVF success. In this study, statistical test was performed between endometriosis characteristic and IVF failure and the result was insignificant with p value of 0,578. This result was not in line with a previous study¹⁷ which explained that endometriosis was associated significantly with IVF failure with p value $< 0,001$. This result was obtained by analyzing the data showing that IVF success rate in women with endometriosis were only 50% compared to non-endometriosis women. This contradiction could be affected by many factors and further research is needed.

Other characteristics studied in this research was POR. Women with POR are likely to fail the IVF. We found a significant association between POR characteristics with p value of 0,027. This result confirms the previous study by Jirge in 2016 which explained that POR is one of the most important factors that affect IVF success⁶. It is stated that 10% of women with POR showed a weak response from gonadotropin stimulations. Another study conducted by Yun et al. in 2017 showed a significant association between POR and IVF failure with p value of 0,019¹⁸.

This study has several limitations such as small sample size and lacking data on medical records. The aforementioned limitations may contribute to our data that indicating different results with the previous studies. ART procedure on each stage were not assessed in this study, and further research is needed with more specific inclusive criteria and bigger sample size.

Conclusion

Age and POR characteristics were associated with IVF failure significantly. Other Characteristics such as BMI, sperm quality, endometriosis, and PCOS did not show significant results. However, characteristics described above should be a consideration in patient who planned to have an IVF treatment.

Article notes

Conflict of Interest The authors declare no conflicts of interest in preparing this article

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Ethical Clearance: Taken

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