Prediction of Pregnancy for Assisted Reproductive Technology:
A Case Study on Intracytoplasmic Sperm Injection Treatment

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Abstract: The treatment for infertility involved emotions and normally very costly. In due to that, some guidance on factors contributed and likelihood of success if they continue the treatment is very helpful for the patients. The aim of this study is to investigate factors influence the success of pregnancy for the Intracytoplasmic Sperm Injection (ICSI) treatment and determine the likelihood of ICSI patient's to become pregnant. *Methods*: Data from the year 2011 to 2015 of an infertility clinic in Malaysia contained 92 records under ICSI treatment. A logistic regression model was used to predict the pregnancy outcome. Mean and median comparisons as well as association test are done to decide on significant factors to be considered. *Results*: Factors of husband's age, husband's smoking status and the interaction of number of grade III oocyte with husband's smoking status are significant (p-value<0.05). Whereas, the number of grade III oocyte is insignificant (p-value>0.05). Based on the Hosmer and Lemeshow test (Chi-square=7.38, p-value>0.05),the logistic regression model fit the data well with Nagelkerke R-Square=0.43. *Conclusion*: The likelihood of getting pregnant using ICSI treatment is dependent on husband's age and smoking status as well as the interaction of number of grade III oocyte with husband's smoking status.

Key words: ART · ICSI · Logistic Regression · Pregnancy Likelihood · Pregnancy Factors

INTRODUCTION

Malaysia aims to be a developed nation by year 2020. In pursuit of this, the Malaysian government has embraced various technological advancements in many fields including medical area. One area in which advances in medical field has received much attention is the treatment of infertility.

The National Institute for Health and Clinical Excellence (NICE) defines infertility as the inability or failure to get pregnant after two years of regular unprotected sex. According to Lyndsay [1] a study conducted by Human Fertilisation and Embryology Authority found that infertility is estimated to affect around one in six or one in seven couples in the United Kingdom which is approximately amounted to 3.5 million people.

Medical technology has been able to come up with various techniques to help childless couples fulfil their dreams of having a child. Currently, there are various forms of assisted reproductive technologies or techniques (ART)to assist human in their plight against infertility, with a certain degree of accuracy.

Hence, the aims of this study are to investigate factors influencing the success of pregnancy for the ICSI treatment and determine the likelihood of ICSI patients to become pregnant.

Factors Influencing Prediction of Pregnancy in ART: Concerning over factors influencing prediction of pregnancy for ICSI treatment, Abha and Siladitya [2] addressed that influences of other factors are also taken into consideration in pregnancy prediction for infertility. According to them, uterus of smoking woman has shown to be associated with infertility when age increase. Science Daily [3] has also highlighted the effects of smoking among mothers and fathers-to-be based on previous study by other researchers. It is found that smoking may cause infertility for both men and women and eventually, it might affect the pregnancy outcome.

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In addition, Deep Health [4] has highlighted the effects of alcohol as one of the causes of fertility problems as it may cause impairments to embryo development, numerous ovulatory dysfunctions as well as increasing level of abnormal shaped sperms. This is also supported by Fortune Baby [5] which stated that consuming alcohol might affect fertility.

Meanwhile, women's age is taken into consideration as one of the factors in predicting pregnancy rate in a study done by Arzu *et al.* [6]. Furthermore, Vera *et al.* [7] also addressed that patients'ages, number of transferred embryos, *egg morphological* were the independent predictors of pregnancy in ART.This is supported by a study done by Marjan *et al.* [8] and was being discussed further by the Southern California Center for Reproductive Medicine [9] which highlighted that women in their twenties have a good chance of becoming pregnant due to relatively greater number of eggs in their ovaries. Meanwhile, women in their thirties will experience a decline of fertility as the fertility rate per month is only about 15%. Furthermore, there is a noticeable decline in the fertility rate, beginning at age 35, which is reduced to 10% per month and there is a sharp decline in a woman's ability to achieve pregnancy over the age of forty.

According to Rachel [10] genetic diseases such as diabetes or obesity can also have negative impact in fertility for both men and woman. A study conducted by Shilpi *et al.* [11] found that obese women would less likely to conceive than women with lower BMIs.

Erman and Oktay [12] concluded that monitoring *Follicle Stimulating Hormone* (FSH) levels during coasting might be helpful in predicting pregnancy outcome.

The accurate prediction of implantation potentials is especially crucial to determine the number of *embryos* to be transferred. According to Loi *et al.* [13], a standard number of three *embryos* are allowed for a transfer. Therefore, in their study, in order to maximize the chances of pregnancy, most of patients with a sufficient number or *embryos*, which are believed to be suitable, would have three *embryos* transferred. Ahmad *et al.* [14] include only patients whonhad two or more number of good quality in their study.

Gultekin *et al.* [15] in their research classify women with five or more oocyte as good responders. this indicates that number quality of oocyte is also factors determining the pregnancy outcome.

Thus, in this study, the factors to be considered in predicting the pregnancy outcomes are patients'

characteristics (Age, BMI, infertility factor, subfertility of wife's final FSH level, alcohol and smoking status of the husband), *egg morphology* (number of grade III *oocyte*) and *embryo* transfer (difficulty of transfer, number of *embryo* transferred).

MATERIALS AND METHODS

Data from year 2011 to 2015 were obtained from an infertility clinic in Malaysia, which contained 92 records under ICSI treatment. The target population were couples who had previously been diagnosed as infertile and agreed to undergone ICSI treatment.

Logistic regression model was implemented for prediction of pregnancy. However, in order to identify which factor(s) to be the independent variables in this model, a mean comparison of the factors between the groups of pregnancy status was conducted using independent sample t-test for normally distributed variables. For median comparison of the factors, Mann-Whitney U test (nonparametric method) was used for non-normally distributed variables. Furthermore, for qualitative variables, an association test based on the likelihood ratio chi-square statistics was done to investigate the presence of statistical association between the pregnancy status and the independent variables (qualitative variables).

For the model selection method, initially the full model was run and the insignificant variables were rejected based on their p-values. In the case when moderating variables were considered and found to be significant, the main effect variable cannot be omitted if one of them turns out insignificant. Hence, extra careful should be given in selecting the insignificant variable to be eliminated. Unlike the stepwise regression where the main effect variable will straight away be deleted based on high p-value. Finally, a test is carried out for eliminated predictor variables, worth rejecting from the model using Likelihood Ratio Test. If the test indicates that the set of eliminated variables are insignificant, therefore the finalized reduced model is accepted.

RESULTS

Factors Explaining the ICSI Outcome: From 92 cases in this study, based on the comparison of means using independent t-test, at 5% of significance level, there was a significant difference in the means of husband's (p-value<0.05) and wife's (p-value<0.05) age as well as

number of grade III oocyte (p-value<0.05) between pregnant and non-pregnant groups. These indicate that husband's and wife's age as well as number of grade III oocyte having a significant effect on the pregnancy outcome for ICSI treatment.

Also at 5% of significance level, there was a significance difference noted in median for smoking status of the husband (p-value<0.05) and difficulty of embryo transfer (p-value<0.05). between pregnant and non-pregnant groups.

For qualitative variables, based on the test of association at 5% of significance level, smoking status of the husband (p-value<0.05) and difficulty of embryo transfer (p-value<0.05) are having significant effect in explaining the prediction of pregnancy outcome for ICSI treatment.

Based on the comparisons in mean and median as well as the association test, factors that have significant influences in the pregnancy status of ICSI treatment were also considered as the factors in the logistic regression model inclusive of the moderating effect. The significant factors were determined through the reduced model of logistic regression for predicting the pregnancy status of ICSI treatment.

Logistic Regression (LR): Initially, full LR was run with variables of smoking status of the husband, difficulty of *embryo* transfer status, husband's and wife's age, difficulty of *embryo* transferred and number of grade III *oocyte* as well as the interaction of variable husband's smoking status and number of grade III *oocyte* predicting the pregnancy outcome (turn pregnant or fail to turn pregnant). Based on the full model, the husband's age, husband's smoking status and the interaction term of variable smoking status of the husband with number of grade III oocyte are significant (p-value <0.05). Other variables that are insignificant were then being omitted and finally, the reduced model was formed.

Based on the reduced model in Table 1, the husband's age, husband's smoking status and the interaction term of variable smoking status of the husband with number of grade III oocyte are significant (p-value<0.05). Otherwise, the number of grade III oocyte is insignificant (p-value>0.05).

Based on the likelihood ratio test, $G^2 = 3.333 < \chi^2_{2,\alpha=0.5} = 5.991$, this concludes that the set of variables (wife's age, difficulty of embryo transfer) does not have any significant effects in predicting pregnancy among patients under ICSI treatment, therefore could be rejected from the logistic model. Hence, it is wise to omit those two variables in the final logistic model as shown in Eq. (1).

The Logistic Regression (LR) Model Adequacy: The classification accuracy of this model is 75%. Hence, the error rate of the model is 25% while the sensitivity and specificity are 68% and 80% respectively. Furthermore, based on the omnibus tests of model coefficients, the logistic regression model of the log odds of pregnancy was significant (Chi-square=34.95, p-value<0.05).

Additionally, Ngelkerke R-Square = 0.43. Thus, this indicates that about 43% of variation in the prediction of pregnancy status is explained by the predictor variables (the husband's age, variable smoking status of the husband, number of grade III oocyte and the interaction term of variable smoking status of the husband and number of grade III *oocyte*) in the reduced model. Other than that, based on the Hosmer and Lemeshow test, the logistic regression model of the log odds of pregnancy is found to fit the data well (Chi-square=7.38, p-value>0.05).

Table 1: Parameter Estimates of Prediction of Pregnancy for ICSI treatment (Reduced Model)

Variables	Est. Coeff. ($\hat{\beta}$)	Std. Error	Wald	df	p-value	Exp($\hat{\beta}$)	95.0% Confidence Interval for EXP($\hat{\beta}$)	
							Lower	Upper
Husband Age	0.173	0.061	7.925	1	0.005**	1.189	1.054	1.341
Grade III Oocyte	-0.269	0.163	2.715	1	0.099	0.764	0.555	1.052
Husband Smoking (1)	-2.975	0.800	12.539	1	0.030*	0.051	0.002	0.100
Smokingh*GIII	-0.147	0.078	5.281	1	0.015*	0.863	0.763	0.964
Constant	-2.434	2.601	0.876	1	0.349	0.088		

Note: Smokingh*GIII is the interaction of variable husband's smoking status and number of grade III Oocyte

*Significant, **Highly Significant

Table 2: Success Rate Estimate under ICSI Treatment

Factors	Coeff.	Couple's Informations			
		1	2	3	4
Husband Age	.173	40	34	41	36
Grade III of Oocyte	-.269	5	3	3	3
Husband Smoking (1)	-2.975	Non-Smoker	Smoker	Non-Smoker	Smoker
Smokingh*GIII	-.147	0	3	0	3
Constant	-2.434	-	-	-	-
Actual Pregnancy Status	-	Pregnant	Not Pregnant	Pregnant	Not Pregnant
Log Odds	-	3.141	-0.775	3.852	-0.429
EXP [Log Odds]	-	23.127	0.461	47.087	0.651
Fitted Response (Success Rate %)	-	0.9586 (95.86)	0.3154 (31.54)	0.9792 (97.92)	0.3944 (39.44)

Success Rate of Pregnancy under the ICSI Treatment: ased on Eq. (1), 4 couples were selected at random and their success rates were estimated in Table 2.

$$Log\left(\frac{p_i}{1-p_i}\right) = -2.434 + 0.173 HUSBAND\_AGE - 0.269 GIII$$
$$- 2.975 SMOKING(H)$$
$$- 0.147 SMOKING(H)*GIII \quad (1)$$

DISCUSSION

Based on the findings, it is shown that the interaction between the number of grade III *oocyte* and husband's smoking status is significant and therefore husband's smoking status is the moderator to number of grade III *oocyte*. This indicates that the marginal effect of smoking status of the husband as well as number of grade III *oocyte* is no longer reliable. Therefore, no conclusive statement to the marginal effect could be made.

The estimated $\hat{\beta}_3 = 2.975$ and $EXP(\hat{\beta}_3) = 0.051$ for husband's smoking status indicates that couple whose husband is a smoker, is less likely to succeed in achieving pregnancy. This may be due to impaired sperm or men's severe infertility that results in failure to get pregnant using the ICSI method. For the moderating effect of smoking status of the husband and number of grade III oocyte, the estimated $\hat{\beta}_2 = -0.269$, $\hat{\beta}_4 = -0.147$ and $EXP[b_4(adj)] = 0.660$ based on Andrew and Jorg [16], this indicates that when number of grade III oocyte increase by 1 unit, for couples with the husband is a smoker, the odds of pregnancy will decrease by 34%. This indicates that even though there are more numbers of grade III oocyte, if the husband is a smoker, this will decrease the likelihood of successful achieving pregnancy. To a medical perspective, this maybe due to a low sperm quality or other men's severe infertility factor that also affect the pregnancy outcome of ICSI treatment.

In this study, the source data were taken from only one of the infertility clinics in Malaysia. Hence, the result of the analysis for this study is insufficient for generalization to a bigger population. Therefore, it is recommended that future researcher could consider a larger sample size and other possible factors in order to study the factors to determine the success in achieving pregnancy under ICSI treatment.

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