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Joint Modeling of *In Vitro* Fertilization Outcomes among A Population of Iranian Infertile Couples: A Historical Cohort Study

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Abstract

Background: Women who undergo *in vitro* fertilization (IVF) cycles should successfully go via multiple stages (i.e., clinical pregnancy, no abortion under 12 weeks, no abortion under 20 weeks, and delivery) to achieve a live birth. In this study, data from multiple IVF cycles and its multiple stages were reanalyzed to illustrate the success factors associated with various stages of IVF cycles in a population of Iranian infertile women.

Materials and Methods: This historical cohort study includes 3676 assisted reproductive technology (ART) cycles. Covariates take into account in this study were women's age, type of infertility (primary, secondary), body mass index (BMI), cause of infertility, history of abortion, duration of infertility, number of oocytes, number of embryos, fertilization rate, semen factors (Spermogram) and having polycystic ovarian syndrome (PCOS) during IVF cycles. Joint modeling was fitted to apply informative cluster size.

Results: Increasing age un women was associated with an increase in the BMI and a positive history of abortion and PCOS, and also, an increase in the number of treatment cycles, while in men was associated with the negative spermogram. With the increase in the number of treatment cycles, the result of the IVF success decreased, but with the increase in the number of embryos, fertilization rate and also, quality and / or quantity parameters of spermogram, we encountered with an increase in the IVF success rate.

Conclusion: It seems that a joint model of the number of treatment cycles and the result of IVF is a valuable statistical model that does not ignore the significant effect of cycle numbers, while this issue is ignored usually in the univariate models.

Keywords: Cluster Analysis, Infertility, *In Vitro* Fertilization

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Introduction

According to the clinical and epidemiological definitions of the World Health Organization (WHO), the prevalence of primary infertility in Iran is 20.2 and 12.8%, in order. Furthermore, the secondary infertility rate is 4.9% (1). In recent years, lifestyle factors have been shown to play an important role in reducing fertility and increasing the use of assisted reproductive techniques (ART) (2). Since infertility can change demographic patterns and have economic, social, and health consequences, different groups of sociologists, epidemiologists, and medical researchers have focused on it (3). The increasing fame of ART, the factor influencing its outcome and the matter of success rate, has led researchers to model the success rate of ART and recognize the factors affecting it in different ways (4-6).

One of the first methods of ART was the "*in vitro* fertilization (IVF)" approach. The process of *in vitro* fertilization (IVF) includes retrieving the oocytes from the female and the sperm from the male and allowing the sperm to fertilize the eggs in laboratory conditions. Then, the embryo(s) is (are) transferred to the uterus,

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and hormones are administered to take place, an implantation (7). A successful IVF must go through several stages successfully [such as chemical pregnancy, clinical pregnancy, non-spontaneous abortion (SAB), and successful delivery] to lead a live birth.

It seems that, success at each stage of IVF can be a predictive tool of the success likelihood of the next stage. In addition, a woman's different cycle relates to pregnancy outcomes, and the female fertility outcome in the present cycle is affected by the outcome of the previous ART cycle. Thus, instead of just considering current cycle data, we also need to consider previous cycle data (8).

ART data analysis methods range widely, from simple binomial tests for intricate models, particularly IVF data. Most ART data studies examine only parts of the data of infertile women (9-12), while it is better to consider the results of the treatments before this treatment. Pregnancy outcomes are often related to a woman's clinical characteristics, making it more likely that women who have previously experienced negative pregnancy outcomes (such as preterm birth, stillbirth, or SAB) will also experience negative fertility outcomes in their current pregnancy. Consideration of early reproductive outcomes, as opposed to just those connected to known pregnancies, is necessary because of the vast range of reproductive outcomes that can demonstrate such intra-woman grouping. A method based on the principles of discrete survival analysis of IVF data with many cycles and various failure kinds for each individual was published by Maity et al. (13). Additionally, the informative cluster size-a measure of the number of cycles an infertile woman completes-relates to the success or failure of the IVF outcome. So it is better to consider it in the analysis to get more accurate results.

The size of the informative cluster is not taken into account in the model of Maity et al. (13). In the present study, a joint modeling of logistic (for outcome of IVF) and Exponentiated exponential geometric regression (EEGR) (for cluster size) was employed to predict the variables affecting the binary outcome of success or failure at various IVF cycle phases while managing the informative cluster size.

Materials and Methods

The Ethics Board of Shahid Beheshti University of Medical Science (Tehran, Iran) approved the present study (IR.SBMU.RETECH.REC.1401.517) and Royan Institute (EC/90/1086). All subjects provided informed consent before the initiation of the treatment. Subjects received assurances that no personal information would be revealed.

Study patients and design

On 3676 cycles of infertile couples who were engaged in ART therapy at the Royan Institute, (Tehran, Iran), a referral infertility center, between April 2011 and March 2015, a historical cohort study was carried out. Only women who had experienced embryo transfer were included in this study. Trained nurses retrieved all the study's variables from the participants' medical records. At each of the four stages, the result variable was success or failure: i. Clinical pregnancy (attendance of an intrauterine gestational sac), ii. Abortion under 12 weeks iii. Abortion under 20 weeks, and iv. Delivery (live birth).

Extracted data of women included age, number of treatment cycles, body mass index (BMI), cause of infertility, history of abortion, duration of infertility, number of oocytes in the last cycle, number of embryos transferred in the last cycle, presence of polycystic ovarian syndrome (PCOS) during IVF cycles, fertilization rate in the last and spermogram (one score sperm-related factor) were all taken into account as covariates in this study.

Statistical analysis

The outcome of each stage, including chemical pregnancy, clinical pregnancy, SAB and delivery, was taken into account as a binary response variable that signifies the success or failure of each stage. The probability of success occurring at a specific stage of the ART cycle could be related to the stage, cycle number, and covariates of interest. Also, the next response variable, which is the number of cycles, is counted and because cycle numbers with disproportionately many ones, we minus 1 in all them and use zero inflated exponentiated EEGR for them. At first, a univariate model was used, and then significant variables were entered into a multiple model (for logistic and EEGR). Finally, the significant variables of multiple models entered into the joint model. The models were applied in accordance with Maity et al. (13) model to determine the impact of covariates on the binary and count outcomes as well as to calculate odds ratios (OR) and 95% confidence intervals (CI). The Statistical Analysis Software (SAS) program version 9.4 "nlmixed" procedures were used.

Results

Demographic data

This study comprised 3636 ART cycles. Following one to three cycles, women were underwent embryos transfer. We present the demographic data of all participants in Table 1.

Univariate models

Table 2 shows the univariate results about logistics and EEGR models. As you can see in this Table, in logistic model, cycle number had a positive significant effect on the failure in each stage after ART [odds ratio (OR) confidence interval (CI 95%): 1.017 (0.988-1.047)]. Duration of infertility had also a positive significant effect [OR (CI 95%): 1.025 (0.004-1.057)]. Although, variables such as number of oocyte, fertilization rate and spermogram had negative significant effect on the failure of each stage of the cycle [OR (95% CI): 0.976 (0.940-1.012), 0.117 (0.061-0.296), 0.134 (0.088-0.282), respectively].

Table 1: Demographics data of our participants

Variable	Frequency (%) or mean ± SD
Age (Y)	31.04 ± 5.02
BMI (Kg/m^2)	26.91 ± 4.10
Infertility type	
Primary	2587 (70.4)
Secondary	893 (24.3)
Duration of infertility (Y)	5.83 ± 4.26
Number of previous treatment	1.67 ± 1.75
History of abortion	0.23 ± 0.63
PCOS	1193 (18.9)
Cause of infertility	
Female	724 (20)
Male	1873 (51.8)
Both	357 (9.9)
Unknown	548 (15.2)

BMI; Body mass index and PCOS; Polycystic ovarian syndrome.

Table 2: The results of univariate logistic and EEGR models

Variable	Logistic model	EEGR model	
	OR (95% CI)	e^{β} (95% CI)	
		Count process	ZI Part
Age (Y)	1.017 (0.988-1.047)	1.519 (1.194-2.323)	0.996 (0.945-1.050)
Cycle number	1.505 (1.061-2.179)		
Type of infertility			
Primary	Ref		
Secondary	1.093 (0.812-1.474)	0.529 (0.280-1.158)	1.519 (0.994-2.323)
BMI (kg/m^2)	1.007 (0.975-1.040)	0.995 (0.002-55.15)	0.347 (0.130-0.664)
Cause of infertility			
Female	Ref		
Male	0.874 (0.616-1.237)	1.169 (0.000-7847)	0.989 (0.818-1.195)
Both	1.172 (0.720-1.909)	0.142 (0.073-1.684)	1.615 (1.269-2.056)
Unknown	0.611 (0.384-0.971)	4.490 (0.168-16.314)	5.226 (2.750-9.933)
History of abortion	1.030 (0.847-1.252)	3.219 (3.040-9.815)	2.278 (1.988-2.611)
PCOS	1.122 (0.804-1.565)	1.721 (1.602-1.864)	0.029 (0.002-0.383)
Duration of infertility	1.025 (0.994-1.057)	1.026 (0.171-6.128)	0.928 (0.909-0.947
Number of oocyte	0.976 (0.940-1.012)	0.221 (0.013-3.760)	1.006 (0.981-1.031)
Number of embryos	0.971 (0.921-1.022)	0.970 (0.932-1.008)	0.881 (0.546-1.002)
Fertilization rate	0.117 (0.061-0.296)	0.220 (0.110-3.220)	0.848 (0.740-0.972)
Spermogram	0.134 (0.088-0.282)	0.785 (0.637-0.968)	0.946 (0.857-1.046)

EEGR; Exponentiated exponential geometric regression, OR; Odds ratio, CI; Confidence interval, ZI; Zero Inflated, and BMI; Body mass index.

Age is directly associated with the cycle number [OR (CI 95%): 1.519 (1.194-2.323)]. As well, the history of abortion and PCOS had the same effect as age on cycle number [OR (95% CI): 3.219 (3.04-9.815), 1.721 (1.602-1.864), respectively]. However, Spermogram had a negative effect on cycle number 0.785 (0.637-0.968).

In zero inflated parts of number cycle, BMI, PCOS, duration infertility and fertilization rate had an opposite effect on having only one cycle number. Moreover, the history of abortion and the number of oocytes were resulted as positively responsible variables than having only one cycle number [2.278 (1.988-2.611), 1.026 (0.981-1.031), respectively].

Multiple models

The results of multiple model are shown in Table 3. In this model, cycle number and duration of infertility had a positive effect on failure in ART [OR (95% CI): 1.141 (1.071-1.282), 1.015 (0.976-1.054), in order], however number of oocytes, fertilization rate and Spermogram had an opposite effect [OR (95% CI): 0.995 (0.940-1.052), 0.333 (0.147-0.769), 0.900 (0.840-1.113), respectively].

In the count part, age, history of abortion and PCOS had a positive effect and Spermogram had a negative effect of the cycle number. In zero-inflated part, history abortion and the number of oocytes had a direct influence, although BMI, PCOS, duration of infertility and fertilization rate had a reverse influence.

Table 3: The result of multiple Logistic and EEGR model

Variable	e^{β} (95% CI)
Logistic model	
Cycle number	1.141 (1.071-1.282)
Duration of infertility	1.015 (0.976-1.054)
Number of oocyte	0.995 (0.940-1.052)
Fertilization rate	0.333 (0.147-0.769)
Spermogram	0.900 (1.008-1.113)
EEGR model	
Count process	
Age (Y)	1.370 (1.170-1.548)
History of abortion	1.569 (1.346-1.720)
PCOS	1.103 (0.995-1.304)
Spermogram	0.140 (0.030-0.985)
ZI Part	
BMI (kg/m^2)	0.465 (0.141-0.651)
History of abortion	1.576 (1.203-1.783)
PCOS	0.090 (0.023-0.142)
Duration of infertility	0.938 (0.910-0.967)
Number of oocyte	1.049 (0.990-1.112)
Fertilization rate	0.882 (0.733-1.062)
EEGR parameter	12.511 (4.608)
Random intercept standard deviation	Estimate (SE)
Logistic part	0.022 (0.012)
Count part	0.237 (0.106)
Zero inflated part	0.166 (0.073)

EEGR; Exponentiated exponential geometric regression, PCOS; Polycystic ovarian syndrome, BMI; Body mass index, and CI; Confidence interval.

Joint modeling

Table 4 shows that estimations of all models that point in the same direction. Parameters, including, age, history of abortion and PCOS history, had a positive effect and Spermogram had a negative effect on the cycle number in count part of EEGR model. According to the results, both parameter, abortion history and oocyte number, had a direct relation and BMI, PCOS, duration of infertility and fertilization rate had a reverse relation with the cycle number in the ZI part. Also, in logistic part of our joint model, cycle number and duration of infertility had a positive effect on the ART failure and the number of oocytes in the last cycle. In addition, fertilization rate and Spermogram had a negative effect on them.

Table 4: The result of joint modeling

Variable	e^{β} (95% CI)	
Logistic submodel[a]		
Cycle number	1.282 (1.089-1.654)	
Duration of infertility	1.009 (0.987-1.030)	
Number of oocyte	0.403 (0.272-0.735)	
Fertilization rate	0.217 (0.104-0.545)	
Spermogram	0.535 (0.108-0.861)	
EEGR submodel		
Count process[b]		
Age (Y)	1.367 (1.172-1.570)	
History of abortion	1.876 (1.404-2.234)	
PCOS	2.904 (2.185-3.211)	
Spermogram	0.137 (0.032-0.428)	
Zero inflation[c]		
Intercept	0.0009 (0.0003-1.395)	
BMI (kg/m²)	0.265 (0.140-1.090)	
History of abortion	1.075 (0.405-3.607)	
PCOS	0.076 (0.023-1.702)	
Duration of infertility	0.555 (0.320-0.966)	
Number of oocyte	1.049 (0.990-1.112)	
Fertilization rate	0.882 (0.731-1.061)	
EEGR parameter	12.511 (4.608)	
Parameter	Estimate (SE)	Wald statistic (P value)
RISD: Logistic part	0.049 (0.009)	
RISD: Count part	0.322 (0.041)	
RISD: Zero inflated part	0.204 (0.023)	
Correlation between a and b	0.421 (0.034)	12.38 (<0.001)
Correlation between a and c	0.650 (0.101)	6.43 (<0.001)
Correlation between c and b	0.512 (0.045)	11.37 (<0.001)

RISD; Random intercept standard deviation, PCOS; Polycystic ovarian syndrome, CI; Confidence interval, [a]; Logistic submodel, [b]; Count process, and [c]; Zero inflation.

The estimation of random intercepts in the models is relatively high which implies the use of mixed model. The correlation among the random intercepts of logistic submodel and the count process was 0.421 (standard error: 0.034). This means that cases with more number of cycles are more prone to experience failure in delivery at some stages, from clinical pregnancy to delivery. The correlation between the logistic and zero inflation sections was 65% that shows a direct association between having only one cycle number and failure in delivery. We observed a positive and significant association between the random effects of count process and zero inflation section.

Discussion

There are several methods for modelling IVF data that contain numerous cycles with various failure categories (11). One way to obtain better estimates of the covariate effects can be obtained by proposing the entire set of IVF data for each woman as opposed to the conventional method, which simply takes into account the first cycle or models each IVF outcome independently.

Studies on this type of data, use informative cluster sizes since it is thought that each infertile woman's cycle count is related to the success or failure of IVF outcomes. Joint modelling was used in this study. The number of cycles and the odds that an IVF procedure will fail were found to have strong positive relationships in this historical cohort study on Iranian infertile women as well, indicating the presence of informative cluster size (14).

Based on the joint modeling, our results show that, the older a woman is, the more cycles are needed to conceive. That is, pregnancy occurs earlier at younger ages due to healthier eggs. In 2019, Ubaldi et al. (15), pointed out in their article that the success of IVF decreases after the age of 35, because maternal age is related to a decline in both ovarian reserve and oocyte qualification. Previous studies have found a strong correlation between women's age and fertility (16-20) which is in agreement with our finding. Also, the history of abortion had a positive relationship with the number of cycles of IVF. This result has been proven in other studies. For example, in endometriosis patients (21), and other types of patients undergoing an IVF cycle (22-25). Having a history of abortion, which may be due to genetic causes or different diseases such as endometriosis, may lead to more IVF treatment cycles.

PCOS is one of the causes of infertility. According to our findings, women with PCOS usually needed more IVF treatment cycles to have the desired number of children. Women with PCOS are more likely to miscarry both after spontaneous and induced ovulation (12). Studies in different years had results consistent with our study (26-29). Of course, some studies had opposite results (8, 30).

In our study, we concluded that Spermogram, i.e. sperm parameters, have a positive relationship with treatment success. The reason is that the healthier sperm, will be formed the healthier embryo, and the pregnancy will be positive as a result. In another study, we see the same result (31, 32).

About BMI, had positive relation to the number of cycles. That means, overweight women need more cycles of IVF treatment to reach a successful result, although there are some studies have reported opposite results. Rittenberg et al. (33) did a systematic review and meta-analysis in 2011 and also showed that BMI has a conflicting role in the IVF outcome and in specific, there is inadequate evidence to define how BMI affects live birth rates. But Veleva et al. (34) concluded in 2008 that being underweight and being overweight increases the chance of miscarriage in IVF. Also, in 2022, Bellver (35) concluded that the IVF result outcome and, overall successful pregnancies were lower in the obese women than non-obese of them. In 2021, Chen et al. (36) linked BMI to gestational diabetes mellitus (GDM) and gestational hypertension but not embryo transfer outcomes following fresh embryo transfer in women receiving their first IVF/ICSI treatment.

Data from multiple IVF treatment cycles were used in this study, along with information about their relationships. Due to the lack of a national registry, past cycles that infertile women may have completed at different infertility clinics were not included in this study.

Conclusion

In this study, we come to the conclusion that the number of cycles or cluster size is informative and has a direct effect on the treatment result.

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Authors' Contributions

M.M., A.K., T.M.; Conceptualization. M.M., A.K., P.A., A.G.; Methodology and Software. M.M., P.A.; Data curation, Writing-Original draft preparation. M.M.; Writing-Reviewing and Editing. All authors read and approved the final manuscript.

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