Original Article

Estimation Methods for Infertility Treatment Success: Comparison of Four Methods

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Received December 2020; Revised and accepted June 2021

Abstract

Objective: To analyze and compare four methods for estimating the chance of treatment success in infertile couples.

Materials and methods: In a retrospective cohort study, information on demographic and clinical features, including age, body mass index (BMI), duration of infertility, semen analysis, previous history of treatment and clinical examination of infertile couples were analyzed. Treatment success (childbearing) was calculated with four methods as live birth ratio, conditional probability and survival analysis (life table and Kaplan-Meyer method) and results are compared.

Results: The fertility ratio for the first treatment cycle was 29.72% which decreased to 23.13% by total treatment cycles. The success rate was 75.4%. With conditional probability calculation at the end of the five treatment cycles. With the life table method in a five-year period, the probability for live birth was 78% and by Kaplan-Meyer method 73.1% and the median of treatment time was 562 days.

Conclusion: Calculation of infertility treatment success rate by only simple live birth ratio of childbearing couples is associated with underestimation. Using the conditional probability method reduces that underestimation, but it is not considered the censored cases in the treatments. It seems life table (as a proxy of survival analysis) presents the closest estimation to clinical facts with considering the repetition of the treatment cycle and the duration of treatment.

Keywords: Fertility; Infertility; Pregnancy Rate

Introduction

Infertility treatment begins with a clinical examination and treatment is selected depending on the couple's condition, and the result is determined after several periods of treatment as pregnancy and childbearing (success) (1). Assisted Reproductive Treatments (ART) increases the chances of fertility (or childbearing) by bypassing the normal fertility process. These treatments are expensive and specific thus the number of attempts and quality of treatment center services are effective in success (childbearing) (2-4). Therefore, the success of infertility treatment depends on various factors.

Researches have shown that treatment duration affects the couple`s childbearing success (5). In the clinics, physicians calculate the ART success (assisted reproductive therapy) in different ways (6). For this reason, different rates could be reported and may be far apart and astonish couples who visit clinics. To estimate the success rate, the live birth ratio of couples who have

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successful treatment to the total number of couples who have been treated has been used (or the number of successes per number of treatment cycles) (7).

For couples whose infertility treatment has failed, it is important to estimate their chances of success in their next attempt (8), and in decision making providing a reliable estimate can prevent waste of time, money and psychological damage (9, 10).

This challenge lies with physicians and patients in deciding to continue treatment and choosing a treatment center, and it needs to be clarified. It seems that the root of the announcement of different percentages of infertility treatment success has two reasons, one is the definition of treatment success and the other is the type of success calculation.

If we provide a definition of success in a consistent and practical way, by comparing the method of calculating success, we can find which method is more appropriate and close to reality. In this paper, we describe and compare four methods of calculating success with data from infertile couples with male factor. The aim of this study is to present an estimation method that is close to the outcome of clinical treatment.

Materials and methods

In a retrospective cohort study, the data and the treatment results of couples who had referred to Avicenna Treatment Center in 2013 (March 2013 to March 2014) for male factor infertility were collected. The samples were selected randomly and in proportion to the number of patients monthly, and finally the data of 232 couples who met the inclusion criteria were selected.

Information on demographic characteristics including age, body mass index (BMI), duration of marriage and infertility, treatment result in other centers and history of infertility in close relatives, and clinical features as semen analysis, characteristics and type of infertility from medical records and the results of the couple's examination were collected.

The success of treatment was defined as the birth of a live baby as a result of assisted reproductive therapy. (i.e. giving birth to a live baby by natural childbirth or cesarean section after at least 30 weeks of pregnancy) (11). Since IUI (intrauterine insemination) and ICSI (intracellular sperm injection) are often used consecutively and frequently, the effect of the two conventional therapies was considered cumulative.

For couples who abandoned their treatment and the fate of their pregnancy was unknown, success was defined as unknown and the duration of treatment was calculated until the stage where there was a definite result. The interval between the first treatment and success was defined as the duration of treatment (11).

The inclusion criteria were as follows: the woman should be normal and healthy in terms of reproductive system and conditions; infertility is diagnosed as male factor and the result of previous fertility treatment must be known; IUI (intra uterine insemination) or ICSI (intracellular sperm injection) treatment or both for couples; the age of women was forty years and less, but the age of men was not limited; treatment must be done with sperm, eggs of the same couple and fresh or frozen embryos of them (autologous material).

The infertility treatment success rate was calculated by four methods: i) fertility ratio, ii) probability calculation (conditional probability) iii) life table and iv) Kaplan-Meyer method (survival analysis) and they were compared.

Childbearing ratio calculated once using the live birth ratio of successful couples in the first treatment period to the total number of couples who participated in the first treatment cycle and again using the live birth ratio of couples who had children after one or more treatment cycle to the total couples participating.

$$\text{birth ratic} = \frac{\text{Success couples}}{\text{Couples in first treatment cycle}} \quad \text{Or} \quad \frac{\text{Success couples}}{\text{Total couples in treatment cycles}}$$

Conditional probability was calculated by calculating the probability of live birth with the condition of failure in the previous five treatment cycle. Base on the sum of the probability of success in each treatment cycle multiplied by the probability of failure in previous treatment cycle. Calculation by life table was performed by using the information of treatment cycles up to five years after the start of treatment and the live birth. The Kaplan-Meier method is used to analyze 'time-to-event' data. An advantage of this method is that the method can take into account some types of censored data, particularly right-censoring, which occurs if a patient withdraws from a study, is lost to follow-up, or is alive without event occurrence at last follow-up. Statistical analysis was performed using STATA statistical software, version 14.2 and SPSS v.18.0

(IBM, NY, USA).

Ethical considerations: The couples signed informed consent to participate in the study. Patient names and personal information such as their address or telephone number were not available to the researcher. The researcher did his best to maintain the confidentiality of the information. The study has been approved by the ethical committee of Avicenna Research Institute (Number 92-46).

Results

In this study, the following conditions were present: a) The couple had children after one or more treatment cycle; b) The couple leaves the corporation for treatment and the result of the treatment is not known; c) The couple did not have children until the end of the study. The oldest couple was treated for about 9 years (intermittently) and the newest couple was treated for 1 year. The couple's genetic examination did not report the possibility of infertility, miscarriage or genetic disease. The cause of infertility in 194 couples (60%) was related to semen quality. Intracellular sperm injection (ICSI) was the first and only treatment in 205 couples (63.5%) and intrauterine insemination (IUI) was the first assisted reproductive therapy in 118 couples (36.5%) that 55 couples of them were later treated with ICSI. The number of treatment cycles was one to 6 and 257 couples (79.6%) had two attempts (treatment cycle). The median treatment time were 297 days (IQR=553) and mean 423 days (SD=484) (Table 1, row 2). The basic characteristics of the couples are given in Table 1.

Childbearing rate by live birth ratio method: In the first attempt (treatment cycle) 96 couples had live birth and the success rate was 29.72%. In the end, after several attempts, 146 couples had children and the success rate of the couples was 45.20%. Totally 631 treatment cycles were performed in the end of study and the live birth ratio was 23.13% (in average) considering the number of treatment cycles.

$$\text{Live birth ratio (per cycle)} = \frac{96 \times 100}{323} \text{ Or } \frac{146 \times 100}{323}$$

$$\text{Live birth ratio (per cycle)} = \frac{146 \times 100}{631}$$

Childbearing rate by conditional probability method: Figure 1 shows the number of attempts (treatment cycles) and success (birth of a baby) due to the repetition of treatment in couples. In this figure, the success rate in each attempt is calculated as a live birth ratio and entered in the red box (last box in right).

The success rate of each treatment cycle is calculated by excluding the couples that are successful or leave the study. The sum of the probabilities of the first to fifth cycles is the total probability and due to the conditionality of the probability of success, at the end of the five treatment cycles, the success rate (childbearing) was calculated to be 75.4%. Table 2 shows how to calculate.

Table 1: The basic characteristics of the couples

Subject	Mean (SD) or Frequency (%)	Median (IQR)
Samples (couple)	323	
Treatment time (day)	423 (484)	297 (553)
Men Age (year)	33.5 (5.6)	33 (7)
Men BMI, kg/m2	26.6 (3.9)	26.9 (3.5)
Duration of marriage (year)	6.26 (3.9)	5 (5)
Duration of infertility (year)	4.76 (3.9)	3 (3)
Treatment history in other centers	12 couple (3.4%)	-
Men with infertility in close relatives	45 (13.04%)	-
The couple's family relationship	54 couple (16.8%)	-
Varicocelectomy	90 (27.9%)	-
Secondary infertility in men	39 (12.1%)	-
Smoker men	44 (13.6%)	-

IQR: inter quartile range, SD: standard deviation

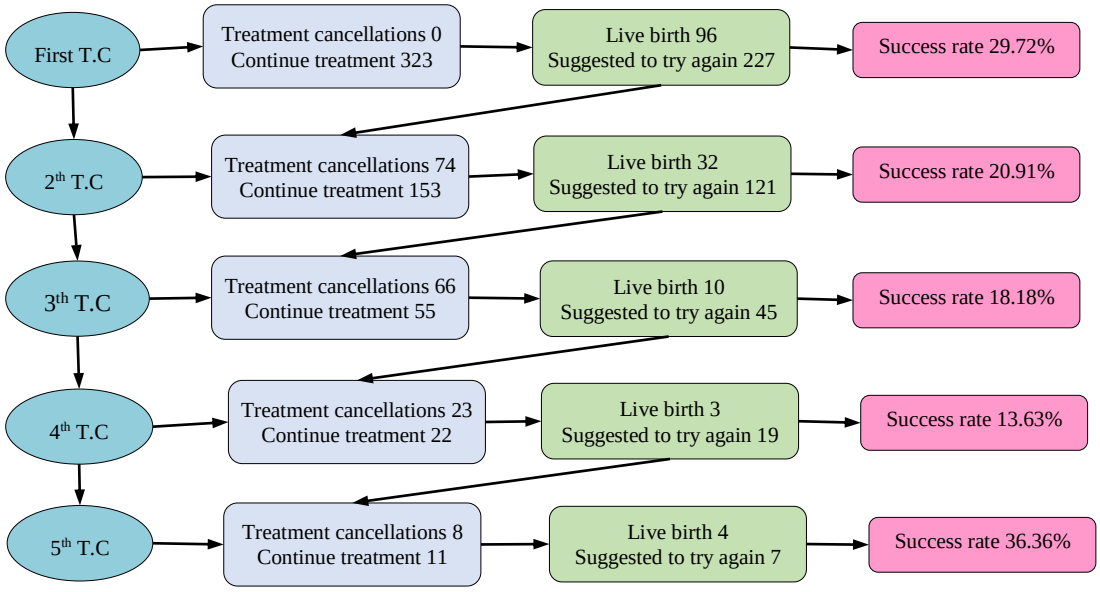

Figure 1: Calculation of success in five attempts and total success rate calculation

Table 2: Calculation by Conditional probability of treatment success in five treatment cycle (based on the Sum of the probability of success in each cycle multiplied by the probability of failure in the previous cycle)

Treatment cycle	Probability
First treatment cycle	(0.2972)
Second treatment cycle	+(0.7028) (0.2091)
3th treatment cycle	+(0.7028) (0.7909) (0.1818)
4th treatment cycle	+(0.7028) (0.7909)(0.1882) (0.1363)
5th treatment cycle	=(0.7028) (0.7909) (0.1882) (0.8637) (0.3636)
Total probability	0.75002

Childbearing rate by life table method (survival analysis): Table 3 shows the waiting time to success for couples who have continued treatment and the waiting time for success in the first to fifth years. In fact, it tells us the chances of success as a life chart. In the last column on the right, the chance of success (childbearing) is calculated at 38% after one year, 53% at the end of the second year, and 73% at the end of the fifth year.

Childbearing rate by Kaplan-Meyer method (survival analysis): The probability of childbearing was calculated using Kaplan-Meyer method and the probability of live birth after 5 year was 73.1%. Also, the median time for childbearing (success) was 480 days (IQR=562), which has (12) low different from the calculated in the non-parametric method (Table 1).

Discussion

The success of infertility treatment is very important for couples and physicians, and in recent years its prediction has received more attention in infertility treatment centers (13).

Table 3: The life table and the chance to live birth in couples who continued the treatment

Year	Duration (days)	Number of cases at the beginning of the period	Censored cases during the period	Exposed cases during the period	Pregnant cases during the period	Cumulative percentage of failed cases at the end of the period	Cumulative proportion of delivery at End of Interval%
1	0-365	323	114	266	91	0.66	34
2	366-730	118	27	104.5	27	0.49	51
3	731-1095	64	18	55	16	0.35	65
4	1096-1460	30	10	25	6	0.26	74
5	1461-1825	14	4	12	2	0.22	78

At the clinic, the most important outcome of an intervention is the success of treatment (here childbearing). Some infertility treatments are injurious in nature thus success is very important by given the cost and time (1, 14). Therefore, in order to estimate the success rate, a method must be used that accurately expresses the probability of success.

Estimation of childbearing by ratio method: In this study, the childbearing rate (success) in the first treatment cycle (attempt) was 29.72% and in case of several attempts, 45.20% which is similar to previous research (12, 15). Success in the first treatment attempt is usually not definite, so this method does not provide a true picture of the treatment success and it seems underestimate it.

Due to the time and repetition of treatment (costs), couples tend to know the probability of their success in having children in order to decide whether to continue their treatment. When the result of the repetition of treatment cycles is considered, the success rate will be rise due to the effect of time, and this rate seems to be closer to reality (15). The childbearing rate with this method (as a successful number to the total number) is to determine the success rate in a period of time (16-19). In fact, the number of attempts and the duration of treatment and the effect of couples who have left treatment have not been considered (20, 21).

When the number of treatment cycles is changed by the number of couples at the denominator of the fraction, the calculation of the success rate changes slightly but is still far from clinical reality. In our study, the success rate considering the number of treatment cycles was 23.3%, which is consistent with other studies (17, 22-24).

The weakness of this method is that when some couples fail, they abandon the treatment and the number of their repeated cycles remains at the denominator of the fraction and the success rate that is calculated is underestimated. There is a fact that the more couples try, the more resistant those to treatment remain in the group, so they are less likely to succeed, and this affects the success rate.

In general, the major drawback of success ratios is the nature of the components of the deductible; That is, which number should be deducted in the numerator and denominator, and this depends on the purpose on which the childbearing rate is defined (25). Ratios do not seem to provide a good estimate of success because treatment time and the number of exposed couples in each treatment cycle are not taken into account (18, 26).

Childbearing estimation by conditional probability: In this method, "success in a treatment cycle" is calculated; in this way, the success rate is calculated with the successful cases in the number of treated samples (exposure) of the same cycle. In our study, after five treatment cycles, the success rate was 75.4%. Therefore, the calculation of this method in a few steps is significantly more accurate than the calculation of ratios and is consistent with clinical reality (27, 28).

However, there are two drawbacks to this method. First, this method clearly takes into account the number of attempts and only the result of success in the calculation, thus the duration of treatment is not taken into account. Second, the outcome of treatment of couples that leave the treatment (censored cases) is not involved in the calculation (in live birth ratio method, these cases are calculated as failures). An example of this is in the last box of attempt 5 in Figure 1. It is observed that by passing through the first to fourth stages of couples' efforts, the probability of success gradually decreases and this shows that the success rate depends on the conditions whose stability defeats the couple's treatment. (The researcher did not find a study that used conditional probability calculation like the method in this article.)

Estimation of childbearing by life table and Kaplan Meyer methods (survival methods): In survival analysis, it is important to have detailed information about the treatment process and the results of interventions (29). In our study, the interval between treatment cycles and pregnancy outcome was recorded in each cycle and live birth information. Also, for couples who left the treatment, the length of treatment was determined and the result was recorded.

Previously, the life table was used for the success rate of egg retrieval (15, 30) and we also created the life table for the success rate of infertility treatment using the data of this study (Table 3). This table shows that the cumulative success rate of couples has increased with each passing year. In the first four years, childbearing increased by 70%, and in later years this trend slowed down and then stabilized. In fact, this table in its second and last columns shows the probability of success and the waiting time until the result of treatment.

The probability of having a child using the Kaplan-Meyer method also estimated the probability of having a child after 5 years at more than 73%, which is acceptable with clinical facts. The median

success time 562 days (CI 95% 381-743) is also more realistic than the median in nonparametric method (Table 1 row 2). This method has already been used by McLernon (31).

In this study, we focused on the calculation methods, and it seems that the survival analysis methods, including the life table and Kaplan-Meyer, show more logical and realistic estimates than the conditional probability and live birth ratio methods.

It should be noted that our study was a single center study and in this case the effect of the treatment team, laboratory and other factors involved in the treatment was the same and the data had little variation. It should be noted that our study was a single center study in which the effect of the treatment team, laboratory and other factors involved in the treatment was consistent and the data had little variation. Therefore, comparing the methods of "estimating childbearing" is less wrong and more reliable (32-34). It is recommended to perform a multicenter study and more samples but with similar protocols for better evaluation (34, 35).

Conclusion

Estimating the success of infertility treatment requires appropriate information from couples, tests and treatment outcome. Some methods of estimating childbearing (the success of treatment) give low estimation. This study showed with increasing treatment time, the number of attempt (treatment cycles) and the probability of success were increased. Given the treatment recurrence and length of treatment time, survival analysis methods show the probability of infertility treatment success close to clinical reality and can better help couples and physicians.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors thank to Professor Hojjat Zeraati for his idea and guidance in the early stages and the Avicenna clinic team for their cooperation.

References

1. Hull MG. Effectiveness of infertility treatments: choice and comparative analysis. Int J Gynaecol Obstet 1994; 47: 99-108.
2. Te Velde ER, Cohlen BJ. The management of infertility. N Engl J Med 1999; 340 (3): 224-6.
3. Leushuis E, van der Steeg JW, Steures P, Bossuyt PM, Eijkemans MJ, van der Veen F, et al. Prediction models in reproductive medicine: A critical appraisal. Hum Reprod Update 2009; 15: 537–52.
4. Bahamondes L, Alma FA, Faundes A, Vera S. Score prognosis for the infertile couple based on historical factors and sperm analysis. Int J Gynaecol Obstet 1994; 46: 311-5.
5. Luke B, Brown MB, Wantman E, Lederman A, Gibbons W, Schattman GL, et al. Cumulative birth rates with linked assisted reproductive technology cycles. N Engl J Med 2012; 366: 2483-91.
6. Meijerink AM, Cissen M, Mochtar MH, Fleischer K, Thoonen I, de Melker AA, et al. Prediction model for live birth in ICSI using testicular extracted sperm. Hum Reprod 2016; 31: 1942-51.
7. Huang JY, Rosenwaks Z. In vitro fertilisation treatment and factors affecting success. Best Pract Res Clin Obstet Gynaecol 2012; 26: 777-88.
8. Meldrum DR, Silverberg KM, Bustillo M, Stokes L. Success rate with repeated cycles of in vitro fertilization–embryo transfer. Fertil Steril 1998; 69: 1005-9.
9. Chambers GM, Sullivan EA, Ishihara O, Chapman MG, Adamson GD. The economic impact of assisted reproductive technology: a review of selected developed countries. Fertil Steril 2009; 91: 2281-94.
10. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National Regional and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLoS Med 2012; 9: e1001356.
11. La Marca A, Capuzzo M, Donno V, Mignini Renzini M, Giovane CD, D'Amico R, et al. The predicted probability of live birth in In Vitro Fertilization varies during important stages throughout the treatment: analysis of 114,882 first cycles. J Gynecol Obstet Hum Reprod 2021; 50: 101878.
12. Ombelet W, Vandeput H, Janssen M, Cox A, Vossen C, Pollet H, et al. Treatment of male infertility due to sperm surface antibodies: IUI or IVF? Hum Reprod1997; 12: 1165-70
13. Benyamini Y, Gozlan M, Kokia E. Variability in the difficulties experienced by women undergoing infertility treatments. Fertil Steril 2005; 83: 275-83.
14. Edwards RG, Brody SA. Principles and practice of assisted human reproduction: WB Saunders Co; 1st edition , 1995.
15. Bouckaert A, Psalti I, Loumaye E, De Cooman S, Thomas K. The probability of a successful treatment of infertility by in-vitro fertilization. Hum Reprod 1994; 9: 448-55.
16. Ombelet W, Vandeput H, Van de Putte G, Cox A,

Janssen M, Jacobs P, et al. Intrauterine insemination after ovarian stimulation with clomiphene citrate: predictive potential of inseminating motile count and sperm morphology. Hum Reprod 1997; 12:1458–63.
17. Lintsen AM, Eijkemans MJ, Hunault CC, Bouwmans CA, Hakkaart L, Habbema JD, et al. Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. Hum Reprod 2007; 22: 2455-62.
18. Van Geloven N, Van der Veen F, Bossuyt PM, Hompes PG, Zwinderman AH, Mol BW. Can we distinguish between infertility and subfertility when predicting natural conception in couples with an unfulfilled child wish? Hum Reprod 2013; 28: 658-65.
19. Veltman-Verhulst SM, Fauser BCJM , Eijkemans MJ. High singleton live birth rate confirmed after ovulation induction in women with anovulatory polycystic ovary syndrome: validation of a prediction model for clinical practice. Fertil Steril 2012; 98 :761-8.e1.
20. Nelson JR, Corson SL, Batzer FR, Gocial B, Huppert L, Go KJ, et al .Predicting success of gamete intrafallopian transfer. Fertil Steril 1993; 60: 116-22.
21. Olsen J, Juul S, Basso O. Measuring time to pregnancy. Methodological issues to consider. Hum Reprod 1998; 13: 1751-3.
22. Uyar A, Bener A, Ciray HN, Bahceci M. Physician experience in performing embryo transfers may affect outcome. Fertil Steril 2011; 95: 1860-2.
23. Porcu G, Lehert P, Colella C, Giorgetti C. Predicting live birth chances for women with multiple consecutive failing IVF cycles: a simple and accurate prediction for routine medical practice. Reprod Biol Endocrinol 2013; 11:1.
24. Erdem A, Erdem M, Atmaca S, Korucuoglu U, Karabaca O. Factors affecting live birth rate in interauterine insemination cycles with recombinant gonadotrophin stimulation. Reprod Biomed Online 2008; 17: 199-206.
25. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. Hum Reprod Update 2011; 17:575.
26. Bouwmeester W, Zuithoff NP, Mallett S, Geerlings MI, Vergouwe Y, Steyerberg EW, et al. Reporting and methods in clinical prediction research: a systematic review. PLoS Med 2012; 9: 1-12.
27. Speirs AL, Lopata A, Gronow MJ, Kellow GN, Johnston WI. Analysis of the benefits and risks of multiple embryo transfer. Fertil Steril 1983; 39: 468-71.
28. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Broekmans FJ, et al. Predictive Value and Clinical Impact of Basal Follicle Stimulating Hormone in Subfertile Ovulatory Women. J Clin Endocrinol Metab 2007; 92: 2163-8.
29. Hosseini M, Mohammad K, Rahimzadeh M, Mahmoodi M. Comparison of survival models in studying breastfeeding duration .Hakim Research Journal 2007; 10: 66-71.
30. Bustillo M, Bhattarai S, Munabi AK, Bender S, Dorfman A, Schulman JD, editors. Life table analysis of pregnancy attainment in an IVF program exclusively utilizing ultrasound-guided oocyte retrieval. VI World Congress of In Vitro Fertilization and Alternate Assisted Reproduction, Jerusalem; 1989.
31. McLernon D, Lee AJ, Maheshwari A, van Eekelen R, van Geloven N, Putter H, et al. Predicting the chances of having a baby with or without treatment at different time points in couples with unexplained subfertility. Hum Reprod 2019; 34: 1126-38.
32. Stolwijk AM, Straatman H, Zielhuis GA, Jansen CA, Braat DD, van Dop PA, et al. External validation of prognostic models for ongoing pregnancy after in-vitro fertilization. Hum Reprod 1998; 13:3542-9.
33. Stolwijk AM, Wetzels AM, Braat DD. Cumulative probability of achieving an ongoing pregnancy after in-vitro fertilization and intracytoplasmic sperm injection according to a woman's age, subfertility diagnosis and primary or secondary subfertility. Hum Reprod 2000; 15: 203-9.
34. Tomassetti C, Geysenbergh B, Meuleman C, Timmerman D, Fieuws S, D'Hooghe T. External validation of the endometriosis fertility index (EFI) staging system for predicting non-ART pregnancy after endometriosis surgery. Hum Reprod 2013; 28: 1280-8.
35. Custers IM, Steures P, van der Steeg JW, van Dessel TJ, Bernardus RE, Bourdrez P, et al. External validation of a prediction model for an ongoing pregnancy IUI. Fertil Steril 2007; 88:425-31.

Citation: Zarinara A, Kamali K, Akhondi MM. **Estimation Methods for Infertility Treatment Success: Comparison of Four Methods.** J Family Reprod Health 2021; 15(3): 179-85.