10.5005/jp-journals-10006-1404

ORIGINAL ARTICLE

Predictive Factors for Pregnancy after Intrauterine Insemination: A Retrospective Study of Factors Affecting Outcome

[1]Azadeh Pravin Patel, [2]Megha Snehal Patel, [3]Sushma Rakesh Shah, [4]Shashwat Kamal Jani

ABSTRACT

Objectives: To determine the predictive factors for pregnancy after stimulated intrauterine insemination (IUI).

Materials and methods: A retrospective analysis of 136 patients undergoing 443 stimulated IUI cycles was done in an attempt to identify significant variables predictive of treatment success. The primary outcome measures were clinical pregnancy and live birth rates. Predictive factors evaluated were female age, duration of infertility, indication for IUI, number of preovulatory follicles, and postwash total motile fraction (TMF).

Results: The overall clinical pregnancy rate and live birth rate were 7.2% and 5.1 per cycle respectively. The mean number of IUI cycles per patient was 3.2, the miscarriage rate was 15%, and the multiple pregnancy rate was 3.1%. Among the predictive factors evaluated, female age (age > 37 years; p = 0.039), the duration of infertility (5.36 *vs* 6.71 years, p = 0.032), and the TMF (between 10 and 20 million, p = 0.003) significantly influenced the clinical pregnancy rate.

Conclusion: The clinical management of the selected infertile couple should be performed in an expedited manner taking into consideration the age of the woman, etiology, and duration of infertility and motile fraction of sperms.

Keywords: Infertility, Intrauterine insemination, Predictive factors.

How to cite this article: Patel AP, Patel MS, Shah SR, Jani SK. Predictive Factors for Pregnancy after Intrauterine Insemination: A Retrospective Study of Factors Affecting Outcome. J South Asian Feder Obst Gynae 2016;8(2):140-144.

Source of support: Nil

Conflict of interest: None

Date of received: 9 Dec 2015

Date of acceptance: 21 Mar 2016

Date of publication: April 2016

[1]Resident (3rd Year), [2]Associate Professor, [3]Professor and Head [4]Assistant Professor

[1-4]Department of Obstetrics and Gynecology, VS General Hospital, Ahmedabad, Gujarat, India

Corresponding Author: Azadeh Pravin Patel, Resident (3rd Year) Department of Obstetrics and Gynecology, VS General Hospital Ahmedabad, Gujarat, India, Phone: +917926563586, e-mail: azadeh.patel511@gmail.com

INTRODUCTON

Intrauterine insemination (IUI) is a simple technique of assisted reproductive medicine, treating infertility by artificial insemination and helping to overcome male subfertility.[1]

A combination of controlled ovarian hyperstimulation (COH) with IUI remains an important option available to an infertility specialist and is a widely used treatment modality for a broad range of indications. Intrauterine insemination is recommended for those couples in whom there is insufficiency of good-quality sperm reaching the upper reproductive tract of the female partner. These may be caused by a lack of fertile cervical mucus (dysmucorrhoea), vaginismus, retrograde ejaculate, mild endometriosis, other mild-to-moderate male factor, and unexplained infertility.[2]

Pregnancy rates per IUI cycle are quite variable in the literature due to differences in the cause and duration of infertility, concomitant usage or omission of ovarian stimulation, sperm preparation techniques, treatment cycles, and number of times IUI is performed during a cycle (single or double).[2-5]

Generally, four cycles of COH/IUI are recommended depending on the female age prior to moving on to assisted reproductive technology (ART) – *in vitro* fertilization (IVF).[4-7]

In all variations of preparation and technique the pregnancy rate ranges between 3 and 26%.[8]

Several prognostic factors with regard to IUI treatment outcome have been identified, and include factors such as patient profile, duration of infertility, type of infertility, stimulation protocol, follicular response, endometrial thickness, timing of IUI, and semen parameters, like postwash motility, morphology, and total motile fraction (TMF).[9-12]

The knowledge that the per-cycle pregnancy rates are not very encouraging combined with the time, effort, and financial implications of such treatment, attempting a COH/IUI cycle could be a challenging decision for the couple. Many couples would opt for one attempt of IVF rather than undergo three to four cycles of COH/IUI. This is especially true for couples traveling long distances seeking treatment in other cities/centers.

MATERIALS AND METHODS

This retrospective, observational study was conducted at a tertiary care center. A total of 136 patients undergoing 443 stimulated IUI cycles between November 2011 and December 2012 were studied.

The study group comprised of couples with male factor infertility, unexplained infertility, minimum-to-mild endometriosis, and anovulation. Patency of at least one tube, confirmed by diagnostic laparoscopy or hysterosalpingography (HSG), was obligatory.

Male factor infertility was defined as semen concentration < 20 million sperms/mL, normal morphology < 30% (WHO criteria), and progressive motility < 50% (A + B) before sperm preparation as per the WHO (1992) guidelines.

Unexplained infertility means when couples for whom the results of a standard infertility evaluation are normal (standard tests includes a normal semen analysis (WHO 1992), ovulatory cycles, and an HSG or laparoscopy showing patent tubes).

Minimal endometriosis score is 1 to 5 and mild endometriosis score is 6 to 15 by the revised AFS criteria.

Exclusion criteria included patients with bilateral tubal blockage, moderate-to-severe endometriosis, and severe male factor infertility, with TMF postwash of < 1 million.

However, patients with a lower sperm count after preparation on the day of IUI were included.

The protocol for ovulation induction included either gonadotrophin only or a combination of clomiphene citrate with gonadotrophin (hMG). In the clomiphene and hMG group, tablet clomiphene citrate 50 mg was started from day 2 of menstrual cycle for 5 days with inj. hMG 75 IU being administered on alternate days from day 5 (days 5, 7, and 9).

In cycles stimulated with gonadotrophin alone, inj. hMG 75 IU was administered on a daily basis from day 5 to day 9. On day 10 of stimulation, assessment of follicular development was performed using transvaginal ultrasound. Further stimulation with gonadotrophin was determined according to follicular response. The aim of stimulation was to achieve a monofollicular response. Once a follicle of > 17 mm size was identified, inj. human chorionic gonadotrophin 5,000 IU (hCG) was given as an ovulation trigger and husband's or donor's or mixed semen inseminated one before ovulation and one after ovulation.

After the procedure, the patient was advised 20 minutes of bed rest. All women were provided luteal phase support with natural micronized progesterone vaginal pessaries for 16 days.

If menstrual cycle was delayed, urine pregnancy test was carried out. When positive, a transvaginal ultrasound was performed 2 weeks later to confirm a clinical pregnancy.

Women were followed till delivery and the neonatal outcome was recorded. The primary end point was clinical pregnancy and live birth rate per cycle.

STATISTICAL ANALYSIS

The variables selected were patient parameters like age of the woman, duration of infertility, type of infertility,and cause of infertility; parameters related to ovulation induction, like number of dominant follicles and endometrial thickness; and laboratory parameters like days of abstinence, postwash motility, morphology, and TMF were recorded.

Of these parameters, the age of the woman, duration of infertility, and days of stimulation were recorded as continuous variables, and their means were compared using the independent t test.

Other parameters were taken as categorical variables and were compared for significant differences using the chi-square test.

A p-value of < 0.05 was considered to be significant.

RESULTS

Overall Pregnancy Rates

The mean number of IUI cycles per patient was 3.2, the pregnancy rate per patient 23.5%, and the pregnancy rate per cycle 7.2% (Table 1).

Both the pregnancy rate per patient and the pregnancy rate per cycle showed a decline after the age of 39 years; however, a significant difference was found only when

Table 1: Pregnancy rates per patient and per intrauterine insemination cycle with reference to the age of the woman

Age (years)	*No. of patients*	*No. of cycles*	*Mean no. of cycles per patient*	*No. of pregnancy*	*Pregnancy rate per patient (%)*	*Pregnancy rate per cycle (%)*
< 30	23	57	2.5	9	39	15.7
30–34	54	167	3.1	14	26	8.3
35–39	45	162	3.6	7	15.5	4.3
40–44	12	47	3.9	2	8.3	2.1
> 44	2	10	5	0	0	0
Total	136	443	3.2	32	23.5	7.2

comparing pregnancy rates per cycle (Table 1). When between-group comparisons were performed, a significant difference was observed in pregnancy rate per patient and per cycle when comparing the < 40 and > 40 years age groups (Table 1). No significant difference was evident in patients younger than 40 years, and no pregnancy occurred in the limited sample of women who were > 44 years.

For Age > 35 Years

p-value equals 0.1932. The association is considered to be not statistically significant.

For Age > 37 Years

p-value equals 0.0394. The association is considered to be statistically significant.

It suggests that pregnancy rates significantly decreases after the age of 37 years.

Of the 443 homologous COH/IUI cycles analyzed during the study period, the mean female age was 30.04 ± 4.295 years (20–43 years).

The cause of infertility was anovulatory in 23.2%, male factor in 20.9%, endometriosis in 8.5%, and unexplained in 45.5% of the patients (Table 2).

The continuous variables were compared using the independent t test. The duration of infertility was found to be significantly associated with the chances of success (5.36 *vs* 6.71 years, p = 0.032) (Table 3).

The categorical variables were compared using the chi-square test. Of all the categorical variables, significant variables affecting outcome were TMF (p = 0.003) and motility (p = 0.04) (Table 4).

From the above observation, the increase in TMF and motility (%) of sperm increases the chances of pregnancy.

As the p-value of both these parameters is > 0.05, the above observation is not statically significant (Table 5).

The overall pregnancy rate per cycle was 7.2% (32/443). Of these, five resulted in abortions (15%) and one was ectopic pregnancy (3.1%). There was one case of multiple pregnancies (3.1%) (Table 6).

Of the 5 abortions, 4 were first trimester and 1 was second trimester. Of 25 pregnancies that went on to term, 23 patients were followed up while 2 patients could not be traced. Fifteen patients underwent caesarean section and eight had normal vaginal delivery. A total of 7 boys and 17 girls were delivered. No major congenital anomaly or neonatal mortality was recorded. The live birth rate/cycle was 5.1% (23/443).

Table 2: Factors affecting pregnancy rates in intrauterine insemination

Parameters	*Pregnancies/cycle*	*Pregnancy (%)*
Infertility etiology		
Anovulation	8/103	7.7
Male factor	4/93	4.3
Endometriosis	2/38	5.2
Unexplained	18/202	8.9
Type of infertility		
Primary	25/358	7.9
Secondary	7/79	8.8

Table 4: Pregnancy rates after intrauterine insemination with respect to some sperm parameters

Parameters	*Pregnancies/cycle*	*Pregnancy (%)*	
Total motile fraction (million/ml)			
< 5	2/110	1.8	Chi-square = 15.91
5–10	3/71	4.2	p-value = 0.003
10–20	13/82	15.8	
20–50	9/91	9.8	
> 50	5/85	5.8	
Motility (%)			
< 60	10/208	4.8	Chi-square = 6
60–80	10/130	7.6	p-value = 0.04
> 80	12/94	12.7	
Morphology (%)			
< 30	1/16	6.25	Chi-square = 0.09
> 30	31/416	7.4	p-value = 0.75

Table 3: Factors affecting the pregnancy rates in intrauterine insemination

	Pregnancy		
Parameters	*Yes*	*No*	*p-value*
Age (years)	29.29 ± 3.90	30.31 ± 7.55	0.384
Duration of infertility (years)	5.35 ± 2.77	6.72 ± 3.88	0.032

Table 5: Pregnancy rates after intrauterine insemination with respect to some ultrasound parameters

Parameters	*Pregnancies/cycle*	*Pregnancy (%)*	*Chi-square*
No. of preovulatory follicles			
1	23/349	6.5	p = 0.303
2	6/78	7.6	
3	3/16	18.7	
Endometrial thickness			
< 6 mm	2/37	5.4	p = 0.787
> 6 mm	30/406	7.3	

Table 6: Pregnancy outcome of the intrauterine insemination cycles

Parameters	*Outcome/cycle (%)*
Pregnancies/cycle	32/443 (7.2)
Live births	23/443 (5.1)
Miscarriages	5/32 (15)
Ectopic pregnancies	1/32 (3.1)
Multiple pregnancies	1/32 (3.1)

DISCUSSION

In our study, we made an effort to determine the prognostic factors that would determine the success of COH/IUI. The variables selected were patient parameters like the age of the woman, the duration of infertility, the type of infertility, and the cause of infertility. Parameters related to ovulation induction included the number of preovulatory follicles and endometrial thickness. Laboratory parameters like postwash motility, morphology, and TMF were recorded.

Among the patient parameters, female age is important as declining oocyte quality associated with increasing age is well documented.[13,14]

Even more effective treatment options like ART-IVF cannot completely overcome the negative impact of age.[15]

In our study, a trend toward reduction in success rate with COH/IUI was noted in women with age > 37 years, although the difference was also statistically significant. However, many studies have documented a significant drop in the success rate beyond the age of 40 years, with reported live births being as low as 1.4%.[16,17]

Put together, for women over 35, COH/IUI as a treatment option needs careful consideration, and for women over 40, IUI is a poor treatment option.

The success rate was significantly lower, with an increase in the duration of infertility (5.36 *vs* 6.71 years, p = 0.032). An earlier study also found a significant decline in the success of IUI therapy as the duration of infertility increased.[12]

However, we were unable to determine any particular cut-off beyond which IUI could be discouraged. With increasing duration of infertility, IUI as an option appears to be less effective.

No difference was noted in the success rate with regard to the type of infertility. Among indications for IUI, the success rate was higher in anovulatory and unexplained infertility patients as compared with endometriosis and male factor infertility, although the difference did not reach statistical significance. The trend toward lower pregnancy rates in endometriosis has been documented in an earlier meta-analysis, with the pregnancy rates reduced to half in comparison with other infertility indications.[9]

The pregnancy rate in our study for male factor infertility was marginally lower than that in previously reported studies.[4,13]

Our overall pregnancy rate with COH/IUI of 7.2% per cycle is low as compared with the results from other studies.[4,13]

Out of all the recorded clinical pregnancies following COH/IUI in our center, only one had multiple gestations, and no case of hyperstimulation was documented during the study period. In our study, a monofollicular response was observed in 78.7% of the cycles. With an increase in the number of preovulatory follicles, a corresponding increase was observed in the pregnancy rates. Studies have shown that the cycle fecundity rates are higher (20–33%) when superovulation protocols are used.[6,10]

However, multiple pregnancy rates, including higher-order pregnancies, also increase with superovulation protocols. Finally, each unit/center needs to decide regarding the stimulation protocols/policies and try to achieve a balance between the quest for a higher success rate and acceptable multiple pregnancy rates.

We found a trend toward a higher pregnancy rate with endometrial thickness > 6 mm; however, the difference was not statistically significant.

The TMF is an important prognostic factor for IUI success. We found a significantly higher pregnancy rate (15.8%) when the TMF was in the range of 10–20 million. The pregnancy rate was lower when the TMF was in the range of 5–10 million (4.2%), with disappointing rates (1.8%) when the TMF was < 5 million. Unexpectedly, the pregnancy rates were also lower with high TMF (> 20 million). In one of the earlier studies, the authors tried to arrive at a cut-off with regard to seminal parameters at which IUI would be of benefit in male factor infertility.[11]

A TMF of < 1 million was associated with poor pregnancy rates. When the TMF was < 5 million, sperm morphology appeared to play an important role. A pregnancy rate of 6.2% was observed with morphology of < 30% as compared with 7.4% with a normal morphology.

Combining the finding of our study and previous reports, we believe that in male factor infertility with a TMF < 5 million, couples should be carefully counseled and the option of ART-IVF should be offered more liberally, especially if the female partner's age is advanced.

We obtained a pregnancy rate/cycle of 7.2% (32/443). The live birth rate/cycle was 5.1%, which is lower than that reported previously.[18,19]

The purpose of our study was to determine prognostic factors for predicting IUI success. We found only three parameters significantly affecting success – duration of infertility, age, and TMF. In an earlier study, the authors found five prognostic factors, namely the number of treatment cycles, the number of preovulatory follicles, age, etiology, and the duration of infertility.[4]

A larger study on similar lines would help identify more predictors and also develop a prediction model for pregnancy following IUI cycles.[20] This could help formulate guidelines and make it easier for couples and clinicians to take important decisions regarding the all-important next step during the course of infertility treatment.

CONCLUSION

COH/IUI is an important treatment option for varied indications, especially when the female age is < 37 years. Definitive prognostic factors for predicting success will help in counseling patients regarding the modality of treatment. Significantly higher pregnancy rates were observed when the duration of infertility was < 5 years, and the TMF was between 10 and 20 million. Low pregnancy rates were associated with poor semen parameters, indicating that COH/IUI is not an effective option in these clinical situations. The overall pregnancy rate per cycle with COH/IUI in our study was 7.2% and the live birth rate per cycle was 5.1%. Our policy of conducting only homologous IUI cycles together with a monofollicular ovulation induction approach is possibly responsible for the comparatively low pregnancy rates obtained. Avoiding twin and higher order pregnancies would be the advantage of such an approach. Many of the identified variables were not shown to significantly affect the outcome. Perhaps, a larger sample size may help in formulating a better predictive model for IUI success. The information could be used by couples and clinicians during counseling to arrive at a decision with regard to their treatment options.

REFERENCES

1. Kerin JF, Kirby C, Peek J, Jeffrey R, Warnes GM, Matthews CD, Cox LW. Improved conception rate after intrauterine insemination of washed spermatozoam from men with poor quality semen. Lancet 1984 Mar 10; 1(8376):533-535.
2. Duran HE, Morshedi M, Kruger T, Oehninger S. Intrauterine insemination: A systematic review on determinants of success. Hum Reprod Update 2002 Jul-Aug;8(4):373-384.
3. Bagis T, Haydardedeoglu B, Kilicdag EB, Cok T, Simsek E, Parlakgumus AH. Single versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: A randomized trial. Hum Reprod 2010 Jul;25(7): 1684-1690.
4. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: An analysis of factors affecting outcome. Hum Reprod 1999 Mar;14(3):698-703.
5. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Engl J Med 1999 Jan 21;340(3):177-183.
6. Dickey RP, Pyrzak R, Lu YP, Taylor SN, Rye PH. Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal semen. Fertil Steril 1999 Apr;71(4):684-689.
7. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. Fertil Steril 2002 Nov;78(5): 1088-1095.
8. Hull MRG. Infertility treatment: Relative effectiveness of conventional and assisted conception methods. Hum Reprod 1992 Jul;7(6):785-796.
9. Hughes EG. Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained subfertility: 'effective treatment' or 'not a natural choice'? Hum Reprod 2003 May;18(5):912-914.
10. Van Rumste M, Custers I, van der Veen F, van Wely M, Evers J, Mol B. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: A meta-analysis. Hum Reprod Update 2008 Nov-Dec;14(6): 563-570.
11. Wainer R, Albert M, Dorion A, Bailly M, Bergère M, Lombroso R, Gombault M, Selva J. Influence of the number of motile spermatozoa inseminated and of their morphology on the success of intrauterine insemination. Hum Reprod 2004 Sep; 19(9):2060-2065.
12. Tomlinson M, Amissah-Arthur J, Thompson K, Kasraie J, Bentick B. Infertility: Prognostic indicators for intrauterine insemination (IUI): Statistical model for IUI success. Hum Reprod 1996 Sep;11(9):1892-1896.
13. Baird DT, Collins J, Egozcue J, Evers LH, Gianaroli L, Leridon H, Sunde A, Templeton A, Van Steirteghem A, Cohen J, et al. Fertility and ageing. Hum Reprod Update 2005 May-Jun; 11(3):261-276.
14. Grøndahl ML, Yding Andersen C, Bogstad J, Nielsen FC, Meinertz H, Borup R. Gene expression profiles of single human mature oocytes in relation to age. Hum Reprod 2010 Apr;25(4):957-968.
15. Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. Hum Reprod 2004 Jul;19(7):1548-1553.
16. Agrawal SK, Buyalon RP. Clomiphene citrate with intrauterine insemination. Is it effective therapy in women above the age of 35 years? Fertil Steril 1996 Apr;65(4):759-763.
17. Frederick JL, Denker MS, Rojas A, Horta I, Stone SC, Asch RH, Balmaceda JP. Infertility: Is there a role for ovarian stimulation and intra-uterine insemination after age 40? Hum Reprod 1994 Dec;9(12):2284-2286.
18. Ibérico G, Vioque J, Ariza N, Lozano JM, Roca M, Llácer J, Bernabeu R. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertil Steril 2004 May;81(5):1308-1313.
19. Ombelet W, Vandeput H, Van de Putte G, Cox A, Janssen M, Jacobs P, Bosmans E, Steeno O, Kruger T. Intrauterine insemination after ovarian stimulation with clomiphene citrate: Predictive potential of inseminating motile count and sperm morphology. Hum Reprod 1997 Jul;12(7):1458-1463.
20. Steures P, van der Steeg JW, Mol BW, Eijkemans MJ, van der Veen F, Habbema JD, Hompes PG, Bossuyt PM, Verhoeve HR, van Kasteren YM, et al. Prediction of an ongoing pregnancy after intrauterine insemination. Fertil Steril 2004 Jul;82(1):45-51.