Prognostic scoring index for intrauterine insemination success among Filipino couples*

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ABSTRACT

Objectives: To identify the clinical factors associated with intrauterine insemination (IUI) success among Filipino couples and incorporate the significant clinical factors in a formula for a prognostic scoring index for the success of IUI.

Methods: This is a review of cases who consulted for infertility and underwent IUI at a tertiary hospital between January 2007 and December 2014. The variables considered for analysis were female age, duration of infertility, etiology of infertility, method of sperm processing, number of preovulatory follicles, total motile insemination count (TMSC), and sperm motility. The outcome measure was determined either by a positive urine or serum beta HCG or a gestational sac on transvaginal ultrasound. Results from the logistic regression analysis were used to develop prognostic scoring index for IUI success. Computed scores were plotted in a Receiver Operating Characteristic Curve and cut off values were determined.

Results: The overall pregnancy rate in this study was 10.7%. Duration of infertility (OR 10.33, 95% CI 3.488-30.602) and sperm motility (OR 5.30, 95% CI 1.830-15.331) showed the strongest significant association with the occurrence of pregnancy. Odds of pregnancy after IUI are likewise increased in female age of < 32.5 years (OR 2.52, 95% CI 1.704-3.734), swim-up method (OR 2.17, 95% CI 1.383-3.415) and TMSC of ≥19.5 million (OR 1.78, 95% CI 1.076-2.954). The odds of successful pregnancy among patients whose duration of infertility is ≤ 2.5 years and who have a sperm motility count of ≥ 67.5 are more than thrice (OR 3.13, 95% CI 0.095-0.990), compared to those with duration of infertility of > 2.5 years. The formulated prognostic scoring index for IUI success was 18.6, with specificity of 91.1%, sensitivity of 39.4%.

Conclusion: Duration of infertility, female age, sperm motility, TMSC and sperm processing method significantly affect the success of IUI success among Filipino couples studied. Using the formula derived, with a sensitivity of 91% and a sensitivity of 39, couples with a score of ≥18.6 are more likely to get pregnant 4 times more than those with a score of less than 18.6.

Keywords: intrauterine insemination, prognostic scoring index, infertility

INTRODUCTION

Infertility, defined as one year of unprotected coitus without conception, affects approximately 10-15% of couples in the reproductive age group.[1] However, a review of population-based surveys estimated the international prevalence of infertility to be 9%.[2] In the Philippines, 14% of women aged 15-49 years old engage in sexual activities but do not bear a child. And, only 0.8% of women of the same population do not really want a child.[3] Involuntary childlessness poses psychological distress, and in turn, poorer quality of life in both male and female partner.[4] The infertile couple experiences depression, grief, guilt, shame, and inadequacy with social isolation.[5] Numerous studies have been geared towards developing approaches to solving this social problem.

Intrauterine insemination (IUI) is a less expensive and less invasive treatment than other assisted reproductive techniques such as in vitro fertilization (IVF) with or without intracytoplasmic semen insemination (ICSI). It is usually indicated in cases of cervical insufficiency, mild endometriosis, mild to moderate male factor and unexplained infertility.[6-8]

Several factors have been associated with the success of IUI, that is, the likelihood of pregnancy. The number of preovulatory follicles,[7-11] total sperm motility count,[6,8,9] and the duration of infertility[6,7,9,10] all correlate with a higher IUI success. Furthermore, in a study by Ahinko-Hakamaa et al in 2007, they found that the impact of woman's age, sperm count, stimulation protocol, and the follicle number on the pregnancy rate is associated with the etiology of infertility.

Duran et al, in 2002, carried out systematic review on the determinants of IUI, wherein, a literature search in the Medline and Cochrane library was studied and analysed. According to the study, the duration of infertility, age of the female partner, history of pelvic inflammation and

*1st Place, 2016 Philippine Obstetrical and Gynecological Society (POGS) Midyear Research Paper Contest, July 05, 2016, Grand Ballroom B & C, Marriott Hotel, Resort Drive, Pasay City

presence of severe male factor have negative impact on outcome, whereas cervical factor, unexplained and anovulatory causes of infertility are more favourable. Moreover, Isa and colleagues in 2014 noted that patients with PCOS, mild male factor and tubal factor have the best success rate.

There were also contradictory results among literature. Montanaro (2001), Duran (2002) and Ashrafi (2013) found that the woman's age has a negative association with the risk ratio of pregnancy. This is in contrast to the study of Iberico (2002) and Yavuz (2013), which noted that the female age was not significant predictor of pregnancy. Furthermore, conflicting results were observed with regards to the body mass index (BMI) of female partner. In a study by Souter et al in 2011 showed no correlation between the BMI of women with the success of treatment cycle of IUI; while Yavuz (2013) negative effect of increasing BMI to the IUI outcome.

Pregnancy rate after IUI varies among studies according to the parameters being studied such as mentioned above. Although many factors have already been identified to affect its outcome, there is still no consensus as to which of these could determine pregnancy success.

Significance of the Project

This was the first local study that investigated multiple factors among Filipino couples and developed a scoring system as to the prediction of IUI success, hence could aid in the proper selection of patients and prognostication of success rate of IUI. It could also serve as a guide in counselling patients with a low probability of a successful IUI to opt to choose the next step to infertility management.

Background Information and Brief Literature Review

Epidemiology of infertility. Male factor and tubal factor both account for 35% of couple infertility, followed by ovulatory dysfunction (15%), unexplained infertility (10%) and other causes (5%). This is in congruence with a literature survey done by Kamel in 2010, showing that the most common causes of infertility are male factor such as sperm abnormalities, female factor such as ovulation dysfunction and tubal pathology, combined male and female factors and unexplained infertility. Hence, these parameters should be the highlighted in the evaluation of infertile couples.

Protocol for infertility work up. Couples who fail to achieve a successful pregnancy after 12 months of regular unprotected intercourse warrant investigation for the cause of infertility. In addition, if the female partner exceeds the age of 35 years, an earlier evaluation should be done after 6 months of unprotected coitus[15].

After a focused history and physical examination of the infertile couple, preliminary investigation should focus on semen analysis, ovarian function determination and tubal patency.

Semen analysis is the cornerstone of investigation for male infertility. It provides information on semen volume, sperm concentration, motility and morphology. The WHO criteria[16] of normal semen was adapted in this study (Appendix I).

Appendix I. WHO: Lower reference limits for semen characteristics[16]

Parameter	Lower reference limit
Sperm volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6per ejaculate)	39 (33-46)
Sperm concentration (10^6per mL)	15 (12-16)
Total motility (%)	40 (38-42)
Progressive motility (%)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3-4)

Ovulatory dysfunction accounts for 15% of cases of infertility and approximately 40% of female infertility. Evidence of ovulation can be documented by measuring mid-luteal serum progesterone or urinary luteinizing hormone. Basal body temperature (BBT) and endometrial biopsy for endometrial dating are no longer recommended for the evaluation of ovulatory dysfunction in an infertile woman.[17] Ovarian reserve function or the function and quality or remaining oocytes, on the other hand, is best documented using assays such as Day 3 FSH and estradiol, and AMH; or antral follicle count (AFC) through transvaginal sonography during the early follicular phase.

Investigation of tubal patency should be done especially if the history is suggestive of tubal disease such as pelvic inflammatory disease, septic abortion, ruptured appendix, tubal surgery or ectopic pregnancy.[1] Hysterosalpingography (HSG) has been used to evaluate tubal patency since 1914, and has remained a gold standard over many decades.[19] Hysterosalpingography is performed in early follicular phase, usually 2 to 5 days after the cessation of menses. A dye is injected through a catheter inserted through the cervix into the uterus. Spillage from one or both tubes is documented via image intensification fluoroscopy.

Intrauterine insemination. IUI involves transfer of processed motile sperm directly into the uterine cavity through a catheter inserted in the cervical os. It is a less expensive and invasive treatment than other assisted reproductive techniques such as in vitro fertilization (IVF) with or without intracytoplasmic semen insemination (ICSI). It is usually the indicated in cases of cervical insufficiency, mild endometriosis, mild to moderate male factor and unexplained infertility.[6-8]

Minimum prerequisites in performing such procedure include the following: the woman must be ovulating, has at least one patent fallopian tube, adequate number of motile sperm and the absence of documented pelvic infections.

The pregnancy rate of IUI varies among literatures. It ranges from as 5% to as high as 70% per patient.[6] Although the success is still debatable, a clinical pregnancy rate per cycle of 10-20% is still an acceptable range.

OBJECTIVES

General objective: to formulate a prognostic scoring index for IUI success among Filipino couples

Specific objectives:

(1) to identify the clinical factors associated with the success of IUI success among Filipino couples
(2) to incorporate the significant clinical factors in a formula for a prognostic scoring index for the success of IUI among Filipino couples
(3) to determine the sensitivity, specificity and accuracy of the derived prognostic scoring index among Filipino couples

METHODS

This study was a review of cases of patients who consulted for infertility and underwent IUI at a tertiary hospital between January 2007 and December 2014.

Inclusion and Exclusion Criteria

The charts of all IUI patients were reviewed and evaluated as to completeness of data available. (1) All couples had at least one-year history of infertility for women aged ≤ 35 years old or at least 6-month history of infertility for women aged > 35 years old and that the minimum prerequisites for IUI was satisfied (the woman must be ovulating, has at least one patent fallopian tube, adequate number of motile sperm and the absence of documented pelvic infections). (2) All patients undergone the same IUI preparation and procedure as described below. (3) Couples who had more than six cycles of IUI were excluded from the study.

Intrauterine Insemination and Procedure

Ovarian Stimulation. Some of the couples underwent ovarian stimulation using either clomiphene citrate or gonadotropin, while a few had none. Ovarian and endometrial responses to stimulation was monitored using transvaginal sonography, until at least one 16 mm-preovulatory follicle was present.

Sperm Preparation. The semen specimen was collected by masturbation into a sterile container after 2-4 days of abstinence from coitus. Sperm processing technique was done either by swim up method or density gradient centrifugation.

Insemination Procedure and Pregnancy Detection. The post-wash semen containing the motile spermatozoa was injected into the uterine cavity, about 0.5 cm from the fundus using either a soft or rigid intrauterine catheter. Success of the IUI cycle was determined either biochemically or ultrasonographically. In this study, either a biochemical pregnancy, that is, a positive pregnancy test performed using urine dipstick or serum beta human chorionic gonadotropin (HCG), performed 2 weeks after the IUI; or a positive gestational sac, 4-5 weeks from the IUI was used as a measure for the success of the IUI cycle.

Data Collection and Statistical Analysis

The variables considered for analysis were the following: female age, duration of infertility, etiology of infertility (female factor vs male factor vs multiple vs unexplained), method of sperm processing (swim up vs gradient), number of preovulatory follicles reaching at least 16 mm in diameter, total motile sperm count (in millions), and sperm motility (%).

The outcome measures of the study were as follows: (1) Clinical Outcome, which is the success of the IUI cycle: determined either by a positive urine or serum beta HCG; or a gestational sac on transvaginal ultrasound; and (2) Research Outcome, which is a prognostic scoring index for IUI success among Filipino couples.

Sample size. Sample size was calculated based on the comparison of pregnancy rate among patients with sperm count of $<1x10^6$ and $\geq 1x10^6$ (Duran, 2002). Assuming that those with sperm count of $<1x10^6$ have a pregnancy rate of 2.1% and those with sperm count of $\geq 1x10^6$, 6.7%, with an α error of 0.05, power of 80% and a 1-tail alternative hypothesis, the sample size required is 338 per group or 676, for 2 groups. Adjusting for 7 more variables in the analysis, with additional 25% for each variable adjusted, the final sample size is 1220.

Statistical Analysis. Each patient was treated as a separate

data unit. Data management and encoding was facilitated using *Microsoft Excel* and *SPSS 12.0 for Windows* programs. Primary outcome was the success of the IUI cycle determined either by a positive urine or serum beta HCG or a gestational sac on transvaginal ultrasound. The descriptive statistics were determined by means of the *SPSS 12.0 frequency, descriptives* and crosstabs procedures. For the comparison between means, *t* tests were performed with *SPSS 12.0*.

A Receiver Operating Characteristic (ROC) Curve was processed to determine the cut off values with highest sensitivity and specificity for prediction of IUI success for the following variables: female age, duration of infertility, number of pre-ovulatory follicles, total motile sperm count and sperm motility. These cut off values were then used to dichotomously categorize the said clinical variables prior to running univariate and multivariate logistic regression analyses.

With the *SPSS 12.0*, univariate and multivariate logistic regression analyses (Table 1) were performed to estimate odds ratios for the independent predictor variables in the study. This included the estimation of the 90% confidence intervals of the event risks.

A Risk Scoring Index (Table 2) was developed for IUI success. The beta coefficients (odds ratio value) of the significant clinical predictor variables derived from the multiple regression model was utilized to develop the risk scoring index. This beta coefficient was converted to a whole number score assigned to each of the parameters as predictor score. Each of the parameters was recoded by multiplying previous frequencies with the respective predictive score. Computed scores were plotted in a ROC Curve and the coordinate points of the ROC curve of the combined scores were subsequently determined. Cut off scores was explored. Sensitivity, specificity and accuracy were computed for each of the assigned cut off scores. Accuracy, positive and negative predictive values and positive and negative likelihood ratios were likewise computed.

Table 1. IUI scoring index

Clinical Variables	Scores
Female age	
< 32.5 years old	1
≥ 32.5 years old	0
Duration of infertility	
≤ 2.5 years	1
> 2.5 years	0
Sperm processing	
Swim up	1
Gradient	0
Sperm Motility	
≥ 67.5%	1
< 67.5%	0
TMSC (in millions)	
≥ 19.5	1
< 19.5	0

Table 2. Coordinates of the Curve

Test Result Variable(s): Score

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
-1.0000	1.000	1.000
.9000	.992	.849
2.0000	.985	.780
2.3500	.985	.779
3.2500	.970	.720
4.1500	.970	.699
4.5000	.970	.678
5.0000	.970	.677
5.9000	.962	.615
6.8000	.962	.610
7.3000	.932	.529
7.6500	.924	.524
8.5500	.924	.484
9.4500	.826	.385
9.8000	.788	.365
10.1500	.773	.359
11.0500	.735	.305
11.9500	.629	.266
12.3000	.621	.249
12.6500	.621	.247
13.5500	.553	.208
14.4500	.538	.195
14.8000	.515	.173
15.1500	.508	.172
16.0500	.477	.140
16.9500	.462	.138
17.3000	.424	.113
17.6500	.409	.109
18.5500	.394	.089
19.4500	.273	.047
19.8000	.174	.028
20.9000	.174	.025
22.8000	.000	.000

Ethical Considerations

This study protocol and all relevant documents was reviewed and approved by the hospital's Institutional Ethics Review Committee. The charts of all IUI patients were reviewed and evaluated as to completeness of data available. The investigators are responsible for the integrity of the data as to the accuracy, completeness, legibility, etc. Each participant was assigned an identification number and only the primary investigators of the study have the access to the list of names. The information that was collected was held with utmost confidentiality. All information about each participant was not be shared to anyone but the primary investigators. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data.

RESULTS

A total of 1228 IUI cycles performed in a tertiary hospital between January 2007 and December 2014 were analysed. The parameters and distribution of variables used to determine IUI success in this study are shown in Table 3.

Women included in the study had a mean age of 34.5 $\pm$ 4.79. The mean duration of infertility prior to the IUI ranged from 6 months to 18 years, with mean of 4.3 $\pm$ 3.20 years. Out of 1228, 81.5% (1002) of the couples had primary infertility while the remaining 18.5% had secondary infertility. The leading etiology for infertility was due to female factor (31%), followed by male and unknown (26%) and finally multiple factors (17%).

A mean of 1.5 $\pm$ 0.85 preovulatory follicles reaching at least 16 mm was present prior to insemination. Most of the sperm preparation was carried out via gradient density versus swim-up (69.85% vs 30.2%). The average sperm motility was 67.4 $\pm$ 21.41%, with a mean total motile sperm count of 26.7 $\pm$ 22.90 million.

Cut off values for female age, duration of infertility, number of pre-ovulatory follicles, sperm motility and total motile sperm count were determined using an ROC Curve. The values with the highest sensitivity and specificity for the prediction of IUI success per variable were as follows: female age of < 32.5 years, duration of infertility of $\leq$ 2.5 years, $\leq$ 3 pre-ovulatory follicles (>16mm), sperm motility of $\geq$ 67.5% and total motile sperm count of $\geq$ 19.5 million.

A univariate logistic regression analysis (Table 4) was performed to investigate the existence of any correlation between the variables and the occurrence of pregnancy. The overall pregnancy rate in our study was found to be

Table 3. Baseline parameters and distribution of variables

Variable	n (%)	Range	Mean $\pm$ SD
Type of infertility			
Primary	1002 (81.6%)		
Secondary	226 (18.4%)		
Female age (in years)		21 – 48	34.5 $\pm$ 4.79
Etiology			
Male factor	319 (26.0%)		
Female factor	382 (31.1%)		
Multiple factors	210 (17.1%)		
Unexplained	317 (25.8%)		
Duration of infertility (in years)		0.5 – 18	4.3 $\pm$ 3.20
Preovulatory follicles (>16mm)		0 – 7	1.5 $\pm$ 0.85
Sperm processing			
Gradient	857 (69.8%)		
Swim-up	371 (30.2%)		
Sperm motility (%)		3 – 98	67.4 $\pm$ 21.41
TMSC (in millions)		0.05 – 372.96	26.7 $\pm$ 22.90

TMSC=total motile sperm count

Table 4. Univariate logistic regression analysis of variables

Variable	Status		Total	Odd Ratio	95% Confidence Interval	
	Pregnant [n (%)]	Not Pregnant [n (%)]			Lower	Upper
Type of infertility						
Primary	114 (11.4)	888 (88.6)	1002	1.48	0.882	2.494
Secondary	18 (8)	208 (92)	226			
Female age						
≥ 32.5 years	76 (17.7)	353 (82.3)	429	2.86	1.978	4.126
< 32.5 years	56 (7)	743 (93)	799			
Etiology						
Male	27 (8.5)	292 (86.1)	319	0.85	1.040	5.244
Female	53 (13.9)	329 (86.1)	382	1.40	1.895	8.731
Unexplained	44 (13.9)	273 (86.1)	317	1.40	1.875	8.833
Multiple	8 (3.8)	202 (96.2)	210			
Duration of infertility						
≤ 2.5years	88 (20)	351 (80)	439	4.25	2.893	6.229
> 2.5 years	44 (5.6)	745 (94.4)	789			
Preovulatory follicles (≥16mm)						
≤3	131 (10.9)	1068 (89.1)	1199	3.43	0.463	25.451
>3	1 (3.4)	28 (96.6)	29			
Sperm processing						
Swim-up	76 (20.5)	295 (79.5)	371	3.69	2.545	5.335
Gradient	56 (6.5)	801 (93.5)	857			
Sperm motility (%)						
≥ 67.5%	105 (15.5)	572 (84.5)	677	3.56	2.296	5.527
< 67.5%	27 (4.9)	524 (95.1)	551			
TMSC (in millions)						
≥ 19.5	83 (17.7)	387 (82.3)	470	3.10	2.135	4.512
< 19.5	49 (6.5)	709 (93.5)	758			

at 10.7%. This was significantly higher in female age of < 32.5 years (17.7%), couples with ≤ 2.5 years of infertility (20%), and in sperm specimen processed through swim-up method (20.5%), with a sperm motility of ≥ 67.5% (%) and total motile sperm count of ≥ 19.5 million (17.7%).

The pregnancy rate of the primary infertility group was noted to be higher (11.4%), compared to the secondary infertility group (8%); however, this was not statistically significant. The same was observed in cycles with 0-3 dominant follicles (10.9%) compared to >3 dominant follicles (3.4%). Among the etiology of infertility, the success of IUI was lowest if multiple factors were present (3.8%), followed by male factor infertility (8.5%), with highest success in female and unexplained causes of infertility (13.9%).

The predictors of IUI success are shown in Table 5. Among the variables evaluated, the duration of infertility (OR 10.33, 95% CI 3.488-30.602) and sperm motility (OR 5.30, 95% CI 1.830-15.331) showed the strongest significant association with the occurrence of pregnancy.

Table 5. Multiple logistic regression analysis of predictive factors of IUI success

	Odds ratio	95% Confidence Interval Lower Upper	
Type of infertility			
Primary	1.27	0.721	2.242
Secondary			
Female age			
≤ 32.5 years	2.52	1.704	3.734
> 32.5 years			
Etiology			
Male	1.28	0.695	2.355
Female	1.06	0.664	1.695
Unexplained	0.76	0.330	1.756
Multiple			
Duration of infertility			
≤ 2.5 years	10.33	3.488	30.602
> 2.5 years			
Preovulatory follicles (>16mm)			
≤3	3.09	0.379	25.153
>3			
Sperm processing			
Swim-up	2.17	1.383	3.415
Gradient			
Sperm motility			
≥ 67.5%	5.30	1.830	15.331
< 67.5%			
TMSC (in millions)			
≥ 19.5	1.78	1.076	2.954
< 19.5			
Duration of infertility by sperm motility	0.30	0.093	0.973

The odds of successful pregnancy after IUI are likewise increased in female age of < 32.5 years old (OR 2.52, 95% CI 1.704-3.734), swim-up sperm processing method (OR 2.17, 95% CI 1.383-3.415) and TMSC of ≥ 19.5 million (OR 1.78, 95% CI 1.076-2.954). Furthermore, the odds of successful pregnancy among patients whose duration of infertility is 2.5 years or less and who have a sperm motility count of 67.5% and above are more than thrice (OR 3.13, 95% CI 0.095-0.990), compared to those with duration of infertility of >2.5 years.

There were five significant independent and a pair variables with interaction derived from the multiple logistic regression. Each of these predictors was assigned with a score of 1 for the positive correlation with the success of IUI and a value of 0 for a negative correlation (Table 5). A constant value derived from the exponent of beta (odds ratio value) for each significant predictor was used as a multiplier for each assigned score (Figure 1). Since there was an interaction between sperm motility of greater then 67.5% and duration of infertility of 2.5 years

IUI score = (Female age* x 2.5) + (duration* x 10.3) + (sperm processing* x 2.2) + (sperm motility* x 5.3) + (TMSC* x 1.8) – (duration of infertility* x sperm motility* x 0.3)

Figure 1. Intrauterine insemination success score calculator

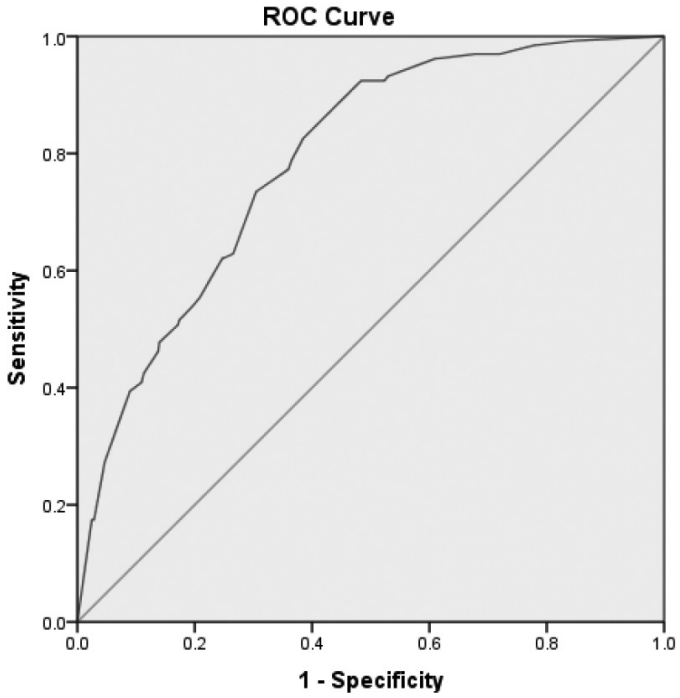

Figure 2. Receiver Operating Characteristic

or less (OR 3.13, 95% CI 0.095-0.990), the product of the mentioned variables and a constant of 0.3 was derived as a subtrahend in the formula for IUI success calculation (Figure 1).

Computed scores were plotted in a ROC Curve (Figure 2) and the coordinated points of the ROC curve of the combined scores were subsequently determined (Table 5). Cut off scores were explored to ascertain the diagnostic cut off point. From the assigned cut off score of -1 to 22.8, the cut off score of 18.6 had the highest specificity of 91.1% and a sensitivity of 39.4%. Using the derived cut off value, the likelihood of having a successful IUI was increase to 4.41x with a score of 18.6.

DISCUSSION

This study highlights the proper selection of patients who could undergo IUI with a higher probability of success. The overall pregnancy rate in this study was found to be 10.7%. This is lower than that of reported by ESHRE Capri Workshop Group in 2009, with a mean pregnancy rate of 12.3% in IUI partner semen specimen; and in FORT Trial in 2014 as reported by Goldman et al with pregnancy rates of 21.6% and 17.3% after 2 cycles of stimulated cycles with clomiphene and gonadotropin, respectively. On the other hand, the reported pregnancy rate was higher compared to that reported by Iberico et al, Kamath et al, Isa et al and Yavuz et al; with pregnancy rates of 9.2%, 8.75%, 10.56% and 4.7%, respectively. Despite these, a 10-20% clinical pregnancy per cycle is still acceptable range regardless of etiology,[2] hence, the pregnancy rate reported in this study is still acceptable.

Conflicting data were found regarding the influence of the type of infertility to the success of IUI cycle. In a retrospective study by Yavuz et al, which investigated 980 IUI cycles, a positive correlation was obtained between potential IUI success and type of infertility. Pregnancy rate in couples with secondary infertility was significantly higher (8.6%) compared to primary infertility group (4%). On the other hand, Iberico et al and Nuojua-Huttunen et al found no statistically significant difference between primary and secondary infertility in terms of pregnancy. This is in congruence with the findings of our study, which showed a higher pregnancy rate in primary infertility group (11.4%) compared to the secondary infertility group (8%), however, not statistically significant (OR 1.48, 95% CI 0.882-2.494).

It has long been documented that there is an inverse relationship between advanced female partner age and fecundity. However, the cut off female age for the success of IUI has yet to be established.[10,22] Iberico et al studied women aged 18 to 43 years and found that the highest odds ratio for pregnancy rates was observed among youngest women (<30 years old) and the lowest among women between 30-34 years of age, with women 40 years or older slightly lower than the youngest women. This trend however did not reach a statistical significance hence they concluded that age does not correlate with the success of IUI. Similar observation was drawn from other studies.[8-10] In a systematic review of literature done by Duran et al, female age, being an indirect indicator of oocyte quality, evidently impacts the IUI outcome. Furthermore, retrospective studies advised against its use in women aged 40 years and above.[7,10] The negative impact of advancing female partner age on the fecundity was also evident in a study by Nuouja-Huttunen et al. They reported a significantly lower pregnancy rate among IUI patients whose female partner aged $\geq$ 40 years (4.1%) as compared to women aged <40 years (13.7%). They also

recommended against the utilization of IUI in couples with female partner aged > 42 years since its success approached nil. Plotting our data on the ROC curve, the cut off female partner age that yielded the highest sensitivity and specificity was 32.5 years. A univariate analysis of our data showed a significantly higher IUI success in women < 32.5 years old (OR 2.86, 95% CI 1.978-4.126), which was still found to be statistically significant even in multivariate analysis (OR 2.52, 95% CI 1.704-3.734).

Many studies have been published on how the etiology of infertility affects the IUI outcome. IUI is usually indicated in cases of cervical insufficiency, mild endometriosis, mild to moderate male factor and unexplained infertility.[6-8] In a retrospective study by Ahinko et al, a total of 1171 cycles from 532 couples were evaluated for the role of infertility etiology on the prognostication of IUI success and found that the pregnancy rate per cycle was highest in the anovulatory infertility group (19.2%) and lowest among women with endometriosis (11.9%). Ashrafi et al, on the other hand, categorized the subjects in their study as following: male factor, ovarian factor, unexplained, tuboperitoneal and multiple factors. Similarly, they found that women with unexplained infertility yielded the highest pregnancy rate (19.9%). This was followed by male factor infertility (18.1%), tuboperitoneal (17.3%), ovarian factor (13.8%) while the multiple factors group had the lowest pregnancy rate (10.6%). In our study, the causes of infertility were grouped into four categories: male factor, female factor, unexplained infertility and multiple factors. The odds of pregnancy was decreased by almost 1.5 times when the indication was for multiple factors, as compared to female factor (OR 1.40, 95% CI 1.895-8.731) and unexplained infertility (OR 1.40, 95% CI 1.875-8.833) alone. This is in congruence with the study of Isa et al wherein the pregnancy rates for PCOS (18.87%) and tubal factor-only (14%) etiologies were significantly decreased when accompanied by other indications for IUI (5.88% and 5.56%, respectively). Although our results did not show a statistical significance when ran in multivariate regression analysis, we could still conclude that multiple factor etiology negatively impacts the success of IUI.

As in other studies,[6,7,9,10,12,22] we observed that the infertility duration negatively affects the success of IUI. However, the precise limits to this, is still debatable – some would recommend a cut off 3 years[6,7] while 5 years or greater in others.[9,10,22] Our results found that pregnancy rate significantly drops when infertility duration reaches more than 2.5 years (5.6%) as compared with 2.5 years or less (20%), which is much shorter compared to previous studies. Multiple logistic regression analysis further revealed an increase in the odds of successful pregnancy by 10 times (OR 10.33, 95% CI 3.488-30.602), the strongest association among all variables studied for this population.

The cut off value for the pre-ovulatory follicle was varied among literatures.[23] For the purpose of this study, we adapted the cut off value 16 mm as cited by Iberico, et al and Nuojua-Huttunen et al. We observed that the pregnancy rate in our report was higher when there were 3 and less pre-ovulatory follicles (10.9%) present prior to insemination as compared to having more than 3 follicles (3.4%). This is consistent with previous studies[7,10,22] wherein they noted no significant increase in pregnancy rates despite an increasing the number of follicles present. However, our study could not make a conclusion on the optimal number of pre-ovulatory follicles since it did not reach a statistically significant value (OR 3.09, 95% CI 0.379-25.153).

Among the variables evaluated in this study, the sperm processing method was the least studied in terms of its association with pregnancy success in IUI. There are four types of semen processing methods that are being carried out in our institution. These are: straight wash, density gradient centrifugation, swim-up and fiber wool filtration.[22] Two of these are of interest in our study: density gradient and swim-up method. Density gradient centrifugation is performed in semen that is normal, oligospermia and moderate oligoasthenospermia, while the swim up method is used in normal, oligospermia, pyospermia and debris > +4. In two meta analyses summarized by Duran et al, density gradient centrifugation had a borderline benefit with regards to the success of IUI as compared to swim up processing method (OR 1.7, 95% CI 1.0-2.9). This is in contrast with the result of this study, wherein the swim up method significantly influence the odds of IUI success by more than thrice (OR 3.69, 95% CI 2.545-5.335) as seen in the univariate analysis. Adjusting for other variables in the multiple regression analysis, a significant association between swim-up method and IUI success was still observed (OR 2.17, 95% CI 1.383-3.415).

Severe male factor parameter is an indication to directly proceed to more advanced assisted reproductive technology such as ICSI and IVF. Hence, proper couple selection that could benefit from IUI, should also include the investigation and screening of male partner as well. Different male parameters have been studied as predictors on the IUI outcome, being the sperm motility after semen processing and total sperm motile count that have been cited most commonly as the predictors of IUI outcome.[6,8,9,10] Although frequently studied, standardization as to the cut off for the ideal sperm parameter that could lead to a positive IUI outcome has yet to be established. A meta-analysis by Duran et al reported significantly higher pregnancy rate in inseminate with $\geq$ 20% motility (14%) compared to <20% motility (5.5%). In 980 IUI cycles studied by Yavuz et al showed a progressive motile sperm ratio of above 50% was noted to be a determinant of IUI outcome (OR 4.18, 95% CI 1.62-10.73). In our study, however, a higher cut off value was observed after the

multivariate analysis, having a threshold of 67.5% motility to significantly affect the IUI outcome (OR 5.30, 95% CI 1.830-15.331).

Processed total motile count has been proven to be a good prognostic indicator for the success of IUI. It has a unique capability of reflecting both sperm concentration and motility, as well as the effects of sperm processing.[24] As reviewed by Duran et al, a threshold of ≥5 million significantly raised the pregnancy rate of IUI from 5.3% to 12.8%, as compared to TMSC of < 5 million. This is much lower than the findings of our study, which suggested a threshold of 19.5 million to significantly increase the chances of a higher pregnancy rate (OR 1.78, 95% CI 1.076-2.954).

In summary, the factors that significantly influence the outcome of IUI observed in this study were female age, duration of infertility, sperm processing method, sperm motility and TMSC. This study also demonstrates the interaction between the duration of infertility and sperm motility, wherein the longer duration of infertility further decreases odds of successful pregnancy despite a favorable sperm motility (≥ 67.5%).

A score of 1 was assigned to each parameter found to positively impact the success of IUI, which include: female age < 32.5 years, infertility duration of ≤ 2.5 years, swim up sperm processing method, sperm motility of ≥ 67.5% and TMSC of ≥19.5. Whereas the parameters noted to negatively impact the success of IUI was assigned with 0. The beta coefficients (odds ratio value) of the significant variables derived from the multiple regression models were the ones utilized as a multiplier on the values assigned per variable. The interaction between the female age and sperm motility was taken into account by subtracting their product and a constant of 0.3 from the sum of all the variables computed.

Computed scores were plotted in a ROC Curve and the coordinated points of the ROC curve of the combined scores were subsequently determined and cut off score were explored. The coordinate with the best specificity (51.6%) and sensitivity (92%) combined is 8.6. However, the authors opted for a higher specificity value since this study aimed to rule in patients that would benefit from IUI. Hence, a cut off value of 18.6 was derived, with a specificity of 91.1% and a sensitivity of 39.4%. Furthermore, using the chosen cut off value of 18.6, the likelihood of having a successful IUI was increase to 4.41 times higher as compared to a score of less than 18.6.

CONCLUSION

Duration of infertility, female age, sperm motility, TMSC and sperm processing method significantly affect the success of IUI success among Filipino couples studied. Using the formula derived from this study, with a sensitivity of 91% and a sensitivity of 39, couples with a score of greater or equal to 18.6 are more likely to get pregnant 4 times more than those with a score of less than 18.6.

RECOMMENDATION

To our knowledge, this study is the first to come up with a prognostic scoring index to evaluate couples as to the success of IUI. There have been numerous studies that reviewed multiple factors that affect IUI success but none came up with a prognostic scoring index. Our report offers an accurate and practical way of counseling patients who consult for infertility and plan for IUI.

With this investigative protocol, a multicenter review of cases can be done and data can eventually be put together for a more robust general population prognostic scoring index. A prospective validation can also be carried out in order to further study the accuracy of the results derived from this retrospective study. ■

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