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Intrauterine insemination in unexplained infertility: Factors associated with successful conception

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Abstract---Infertility is the inability of a couple to conceive after one year of regular and unprotected intercourse. It is a common problem with a global prevalence rate of approximately 9%; in developing countries, this may affect up to 25% of couples [1, 2]. In 2010, an estimated 48.5 million couples worldwide were unable to have a child after five years of trying [2]. According to prior psychosocial studies, it is known that both infertility and its treatment can lead to emotional and psychological stress, and thus threaten the quality of life for infertile couples [3]. Moreover, fertility treatments may not be offered early enough and so those with infertility suffer for a potentially longer duration. Being a prospective study, the completeness of the data is a strong point of this study. All eligible patients fulfilling the inclusion and exclusion criteria were enrolled to avoid sampling bias.

Keyword---intrauterine, insemination, unexplained infertility, successful conception.

Introduction

Infertility is the inability of a couple to conceive after one year of regular and unprotected intercourse. It is a common problem with a global prevalence rate of approximately 9%; in developing countries, this may affect up to 25% of couples

[1, 2]. In 2010, an estimated 48.5 million couples worldwide were unable to have a child after five years of trying [2]. According to prior psychosocial studies, it is known that both infertility and its treatment can lead to emotional and psychological stress, and thus threaten the quality of life for infertile couples [3]. Moreover, fertility treatments may not be offered early enough and so those with infertility suffer for a potentially longer duration. There are both male and female factors that account for infertility. The various male factors are disorders of spermatogenesis, obstruction in the reproductive tract, disorders of sperm motility and sexual dysfunction. The factors in the female partner contributing to infertility include disorders of ovulation, blocked fallopian tubes, endometriosis and less commonly immunologic and other factors.

Unexplained infertility or idiopathic infertility refers to the failure of a couple to conceive in whom no definite cause for infertility can be identified. Couples should undergo a semen analysis, ovulation testing and assessment of tubal patency before a diagnosis of unexplained infertility is made. However, even the most sophisticated diagnostic assessment cannot reveal all possible abnormalities. Unexplained infertility accounts for about 30-40% of the total cases of infertility [4, 5]. The term 'unexplained' is not only an admission that the cause of infertility is unknown but also that the couple may not be infertile at all. It appears to represent either the lower extreme of the normal distribution of fertility, or it arises from a defect in fecundity that cannot be detected by the routine infertility evaluation. Unexplained infertility poses a great challenge to both the patients and the treating physicians. The treatment is empiric because there is no 9 correctable abnormality.

The treatment options available are expectant management with lifestyle modification and timed intercourse (TI); ovarian stimulation (OS) with intrauterine insemination (IUI) and in vitro fertilization (IVF). There is much controversy about the selection of appropriate management for these couples. Controlled ovarian hyperstimulation (COH) with IUI is widely used in cases of unexplained infertility before resorting to more invasive options such as IVF. It can be performed without expensive infrastructure and is a safe treatment with minimal risk of ovarian hyperstimulation. However, a major concern with the former is the multiple pregnancy rate consequent to the development of multiple follicles. By using mild ovarian hyperstimulation and strict cancellation policies, multiple pregnancy rates can be kept to approximately 10% without reducing pregnancy rates [6].

Literature reports indicate pregnancy rates ranging from 3% to 19% per cycle [7]. Potential factors influencing the success rate of IUI include: male infertility factors (semen analysis), female infertility factors (duration of infertility, age, ovarian reserve, etiology), and techniquedependent factors (homologous or donor insemination, number of cycles, number of inseminations per cycle, follicle development, type of stimulation received and total dose administered). Global and national data are conflicting with regard to the extent of influence, if any, exerted by these factors as definitive determinants of success and the magnitude to which each factor contributes to positive pregnancy are still unequivocal. Need for this study Studies on this subject reported from India being few in number, the present study was designed to evaluate the pregnancy rate at the study institute and factors that may predict successful conception in women

undergoing OS and IUI. Identification of characteristics associated with successful treatment outcomes will in turn facilitate effective counseling and treatment planning. Hence the present study aimed to determine the pregnancy rate per cycle following OS and IUI in women with unexplained infertility and to evaluate the factors associated with successful conception.

Material and Methods

The present prospective observational study was conducted in department of gynecology, Fernandez Hospital, Hyderabad, Telangana. Study population was women diagnosed with unexplained infertility and planned for OS + IUI. This study was conducted from march 2018 to august 2019.

Inclusion criteria

- Regular menstrual cycles
- Partner's semen analysis normal
- Patent fallopian tubes by hysterosalpingogram or laparoscopy

Exclusion criteria

- Previous failed IVF
- Moderate or severe endometriosis by laparoscopy or endometrioma(s) on× ultrasound Donor insemination as it is not performed at the study institute.

Methods

Couples presenting to the gynaecology outpatient with complaints of inability to conceive were assessed for the cause of infertility. Women diagnosed with unexplained infertility (inclusion criteria above) were recruited for the study after obtaining informed consent. The presence of a regular menstrual cycle in itself is a fair indicator of regular ovulation, and the chances of anovulation in a woman with a regular menstrual cycle are low [8,9];

Objective assessment

Such as ultrasound documentation of ovulation or luteal phase serum progesterone was not routinely performed. The study variables included age, BMI, duration of infertility, menstrual history, obstetric history, and investigations for infertility, treatment details including OS medication and number of follicles, IUI details and semen parameters post-process (proforma). OS was commenced with oral (clomiphene, letrozole, tamoxifen or anastrozole singly or in combination) and/or injectable (gonadotropins i.e. FSH or FSH + LH combination) agents and follicular monitoring was carried out by transvaginal ultrasonography. When the largest follicle measured around 18-20mm, ovulation was triggered with injection hCG 5000IU given intramuscularly. When there were >4 intermediate sized follicles of ≥14 mm, injection triptorelin 0.2mg was given subcutaneously instead of hCG. Cycle cancellation was advised when the number of dominant follicles exceeded 3. After 24 to 36 hours of ovulation trigger, fresh sample of semen from the woman's partner was collected and prepared by double density gradient

method. The male partner was advised 1-2 days of sexual abstinence prior to the IUI procedure. Pre- and post- wash semen analysis was done according to WHO 2010 guidelines. The processed semen (0.5ml) was inseminated into the uterine cavity under transabdominal ultrasound guidance. Luteal phase support with progesterone vaginal suppository (400 mg/day) was offered for 14 days post-procedure. Transvaginal ultrasound was performed 3 weeks after the IUI procedure to confirm pregnancy, its location and number of gestational sacs. Embryonic cardiac activity was confirmed 3 weeks later. Ectopic pregnancies or pregnancies of unknown location that occurred following treatment were followed up and managed as per the institute protocol.

Sample size

Sample size was calculated to be 154 with Z value of 1.96, margin of error assumed to be 5%, based on the success rate of 11.3% from previous Indian studies [10, 11]. n= Z1-α/2 2 p(1-p) d 2 p = expected proportion d = absolute precision 1-α/2 = desired confidence interval n= 1.962 x 0.113 x (1-0.113) $(0.05)^2$.

Statistical analysis

The success of IUI in the study was measured as cycle pregnancy rate as a point estimate and 95% confidence intervals around the point estimate. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non-normally distributed quantitative 35 variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams such as bar diagrams, pie diagrams and box plots. All quantitative variables were checked for normal distribution within each category of explanatory variables by using visual inspection of histograms and normality Q-Q plots. Shapiro-Wilk test was also conducted to assess normal distribution. Shapiro-Wilk test p value of >0.05 was considered as normal distribution. For non-normally distributed quantitative parameters, medians and IQR were compared between those who conceived and those who did not using Mann Whitney U test (2 groups). Categorical outcomes were compared using Chi square test /Fisher's exact test. If the expected number in any of the cells was < 5, Fisher's exact test was used. Logistic regression analysis was carried out to evaluate the predictors associated with conception following IUI. A p value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Results and Observations

The study comprised 124 patients with unexplained infertility who underwent ovarian stimulation + IUI during the study period. The age of the female partner ranged from 21 to 41 years, averaging 30.4 ± 4.79 years. The age of the male partner ranged from 22 to 50 years, averaging 34.73 ± 4.9 years. Majority (48%) of the women had normal body mass distribution; 30% were overweight and 24% were obese. Most of the couples (59.7%) in this study had primary infertility. Among the 50 couples with secondary infertility, 18 had one or more living children while 6 had a history of recurrent pregnancy loss (≥3 losses). The duration of infertility was ≤5 years in 77.4% of the couples. Forty-three (34.7%) of

these 124 women had undergone one or more cycles of IUI treatment prior to recruitment into the study. During their infertility evaluation in the past, 29 of them had undergone hysteroscopy (4 polypectomy and 1 septal resection) and 28 had undergone laparoscopy (3 had minimal to mild endometriosis).

Conception

The 124 couples who were part of the study underwent a total of 224 IUI cycles. The primary and secondary outcomes were analyzed with 224 as the denominator. Of the 224 IUI cycles, 36 resulted in a pregnancy accounting for a cycle pregnancy rate of 16.1% (95% CI: 11.5-21.5). Among the 124 couples who participated in the study, 34 (27.1%) women conceived with two of them having two pregnancies each. Most conceptions occurred in the first or second cycle of IUI with only one conception recorded in 32 attempts in women who underwent 4 or more cycles. The conception rate per cycle in the first two cycles was significantly higher than that in cycles 3-6 (19.9% versus 8.2%; p = 0.026). The potential factors influencing success of IUI were analyzed. Age of the female partner The median age of the female partner was 31 years (IQR 27.8, 35.0) in those who conceived and 30 years (IQR 27, 33) in those who did not. This difference was not statistically significant 48 (Mann Whitney U test p value 0.409). There was no difference in conception rates between age groups (Table 2).

Age of the male partner

The median age of the male partner was 33.5 years (IQR 31.0, 37.3) in the couples who achieved conception and 34 years (IQR 32, 38) in those who did not. This difference was not statistically significant (Mann Whitney U test p value 0.458)

BMI

The median BMI of the female partner was 25 years (IQR 23.2, 30.0) in those who conceived and 25 years (IQR 22.4, 27.8) in those who did not. This difference was not statistically significant (Mann Whitney U test p value 0.490).

Duration of infertility

The median duration of infertility was 3 years (IQR 2.0, 5.3) in those who conceived and 3 years (IQR 2, 5) in those who did not. None of the 3 IUI cycles performed in couples with infertility duration >15 years resulted in a conception.

Ovarian stimulation

Majority (64.7%) of the stimulation regimes involved a combination of oral and injectable drugs. Gonadotropins were used for ovarian stimulation in a total of 155 cycles; the median requirement was 300 units (IQR 225, 450). There was no significant difference in conception between different stimulation regimes. In the combination (oral + injectable) group, the mean gonadotropin dose was higher for overweight (454.89 ± 315.9 IU/cycle; p<0.005 and obese (362.9 ± 213.1 IU/cycle; p = 0.085) women than women with normal BMI (286.4 ± 169.5

IU/cycle). Day of ovulation trigger No significant difference was noted with regard to the success of IUI based on the day of the menstrual cycle on which ovulation was triggered.

Number of dominant follicles on the day of ovulation trigger

Conception rates increased with increasing number of follicles. Eight women with ≥3 dominant follicles proceeded with IUI despite explaining the risks and advising cycle cancellation; 2 of them conceived singleton fetuses.

Endometrial thickness on the day of ovulation trigger

The endometrial thickness was ≥7 mm on the day of ovulation trigger in 85.7% of the cycles. The median endometrial thickness was 8.1 mm (IQR 7.2, 9.3) in those who conceived and 8 mm (IQR 7.18, 9) in those who did not. This difference was not statistically significant (Mann Whitney U test p value 0.552). The conception rates did not differ significantly between women with endometrial thickness ≥7 mm compared to those with thickness.

Ovulation trigger

Eighteen (8.0%) women were administered triptorelin to trigger ovulation as they had ≥3 dominant follicles or multiple intermediate-sized follicles. In the rest, ovulation was triggered with 5000 units of intramuscular hCG injection. There were no documented cases of ovarian 57 hyperstimulation. There were equal conception rates (~16%) in the group that received hCG and the group that received triptorelin as ovulation trigger. Time interval between ovulation trigger and IUI In 67% of cycles, IUI was performed 36-40 hours after trigger of ovulation. The conception rates were not significantly different in women who underwent IUI between 24-28 hours after ovulation trigger compared to those who had the procedure between 36-40 hours post-trigger. Vaginal micronized progesterone suppositories (400 mg per day) were offered for luteal phase support to all women; 12 of them who preferred oral progesterone were prescribed dydrogesterone (20 mg per day).

Post-wash motile sperm count

The median post-wash motile sperm count was 42 million (IQR 33.5, 59.0) in those who conceived and 42 million (IQR 26, 58) in those who did not. This difference was not statistically significant (Mann Whitney U test p value 0.248). IUI was carried out with a soft catheter in all cases except 7 in whom a rigid catheter with stilette was required for negotiating the cervical canal and the lower uterine cavity. On analyzing the effect of potential factors influencing IUI success by logistic regression (table 12), development of ≥2 follicles and post-wash motile sperm count >30 million were associated with twice the odds of conception than monofollicular development and post-wash motile sperm count 30 million were significantly associated with conception with aOR of 4.668 (95% CI: 1.176-18.529; p = 0.028) and 11.705 (95% CI: 1.431-95.772; p = 0.022) respectively.

Pregnancy outcomes Fig.1: Flow diagram depicting the outcomes of IUI conceptions

Conception (N = 36)

Ectopic pregnancy
- N = 3
- Medically managed

Pregnancy of unknown location
- N = 2
- Resolved spontaneously

Intrauterine pregnancy
- N = 31
- Live birth – 15
- Ongoing pregnancy – 7
- Miscarriage – 9

Nine pregnancies ended in a miscarriage in the first trimester. There were no preterm births. All babies were delivered with good Apgar scores and birth weights ranging from 1950g to 3220g. There were no stillbirths or neonatal deaths. There were three sets of twins: one was delivered at 36 weeks, one was a case of vanishing twin with delivery of a single baby at 39 weeks; and the third is an ongoing pregnancy. There were no higher order multiples in the study population.

Table 1
Socio-Demographic Profile of Study Population

VARIEBLES	NUMBER		PERCENTAGE	
AGE GROUP	MALE	FEMALE	MALE	FEMALE
20-24	2	13	1.6	10.5
25-29	10	39	8.1	31.5
30-34	60		48.3	36.3
35-39	32	45	25.8	18.5
≥40	20		16.2	3.2
		23		
		4		
BMI				
<18.5	2		2	
18.5-24.9	60		48	
25-29.9	37		30	
30-39.9	24		19	
≥402	1		1	
TYPE OF INFERTILITY				
PRIMARY	74		59.7	
SECONDARY	50		40.3	
DURATION OF INFERTILITY				

≤5	96	77.4
6-10	21	16.9
11-15	5	4
16-20	2	1.7

Table 2
Number of IUI attempts, Associations of conception with Age, BMI & duration of infertility

Cycle number	Number of patients starting cycle	Pregnancies	(%)
1	84	17	20.2
2	67	13	19.4
3	41	5	12.2
4	21	0	0.0
5	8	1	12.5
6	3	0	0.0
Female Age group	n	Conception – n, (%)	
20-24	25	3, (12.0)	Chi square – 1.186; p = 0.880
25-29	69	10, (14.4)	
30-34	81	13, (16.0)	
35-39	45	9,(20.0)	
≥40	4	1, (25.0)	
Female Age group	n	Conception – n, (%)	
20-24	4	0, (0.0)	Not applicable
25-29	20	3, (17.0)	
30-34	103	17, (16.5)	
35-39	59	12, (20.3)	
≥40	38	4, (10.5)	
BMI			
<18.5	3	0, (0.0)	
18.5-24.9	109	18, (16.5)	
25.0-29.9	65	8, (12.3)	
30.0-34.9	44	10, (22.7)	
≥40	3	0, (0.0)	
Duration of infertility in years	n	Conception – n, (%)	
1-5	163	26 (16)	Not applicable
6-10	45	7(15.5)	
11-15	13	3(23)	
16-20	3	0	

Table 3
Conception rates with different OS regimes

Agent used for OS	Conception – n, %
Clomiphene (n = 15)	4, (26.7)
Tamoxifen (n = 20)	2, (10.0)
Letrozole (n = 31)	4, (12.9)
Clomiphene + tamoxifen (n = 2)	0, (0.0)
Letrozole + tamoxifen (n = 1)	0, (0.0)
Human menopausal gonadotropin [HMG] (n = 10)	2, (20.0)
Clomiphene + follicle stimulating hormone [FSH](n = 3)	0, (0.0)
Clomiphene + HMG (n = 36)	6, (16.7)
Tamoxifen + FSH (n = 6)	1, (16.7)
Tamoxifen + HMG (n = 47)	6, (12.8)
Letrozole + FSH (n = 3)	1, (33.3)
Letrozole + HMG (n = 41)	9, (22.0)
Anastrozole + HMG (n = 1)	0, (0.0)
Clomiphene + tamoxifen + HMG (n = 8)	1, (12.5)

Table 4
Association of Conception with Ovulation Trigger Day & Number of Dominant Follicles

Day of ovulation trigger	Conception – n, %	
<10 (n=17)	2, 11.8	Chi square – 1.523, p value = 0.677
10-12 (n=117)	18, 15.4	
13-15 (n=75)	12, 16.0	
>15 (n=15)	4, 26.7	
Number of dominant follicles	Conception – n, %	
1 (n = 117)	13, 11.1	Chi square – 8.637, p value = 0.035
2 (n = 76)	13, 17.1	
3 (n = 23)	8, 34.8	
4 (n = 5)	1, 20.0	
5 (n = 2)	1, 50.0	
6 (n = 1)	0, 0.0	

Table 5
Univariate binary logistic regression analysis of factors affecting conception

Parameter	OR, 95% CI; p value (all cycles)	OR, 95% CI; p value (first cycle)
Age of female partner	1.029, 0.954-1.109; 0.458	1.011, 0.904-1.130; 0.847
Age of male partner	0.981, 0.698-1.378; 0.911	0.948, 0.838-1.073; 0.399
BMI	1.023, 0.949-1.103; 0.551	0.974, 0.852-1.112; 0.692
Secondary infertility	1.579, 0.769-3.240; 0.213	1.104, 0.374-3.262; 0.858
Duration of infertility <5 years	0.980, 0.442-2.171; 0.960	0.724, 0.173-3.029; 0.658

Gonadotropins for OS	1.189, 0.539-2.625; 0.668	4.529, 1.191-17.225; 0.027

Discussion

This study aimed to determine the pregnancy rate per cycle following IUI in women with unexplained infertility and to evaluate the factors associated with successful conception. The cycle conception rate was 16.1% and the cumulative pregnancy rate 27.1%. Multifollicular development and post-wash motile sperm count >30 million were significantly associated with successful conception following IUI. Gonadotropin usage for OS and post-wash motile sperm count >30 million were significant predictors in the first IUI cycle. Conception rates and multiple pregnancy rates Literature reports of conception rates per cycle range from 10% to 20% [20, 34, 51, 52, 59, 61] and cumulative pregnancy rates range from 27% to 39% [14, 23, 48, 52, 58]. The findings of the present study were similar to the conception rates reported by other researchers from India.

The rate of conception was highest in the first two IUI cycles (~ 20%) and declined thereafter. A similar observation was made in another Indian study wherein most women conceived during the first and second cycles and none during the third [11]. Caucasian data suggests that 3 cycles of IUI with OS can be beneficial for many couples with unexplained infertility [12, 13, 14]. There were a total of 36 conceptions in the present study, of which 3 were twin gestations (one was a vanishing twin that reduced to a singleton). Excluding the first trimester pregnancy losses, the multiple pregnancy rate was 9.1% (2/22) per ongoing pregnancy. While earlier studies reported higher rates between 13.3% and 23.5% [15, 16, 17], the more recent 2015 multicentric trial from the Netherlands found 7% multiple pregnancy rate per ongoing pregnancy [18]. In the meta-analysis by van Rumste et al, the absolute multiple pregnancy rate was 0.3% after monofollicular and 2.8% after multifollicular growth [19].

The corresponding rates were 7.6% and 8.7% respectively in our study. All 3 twin gestations were observed in women who had received gonadotropins for OS but none of them had developed >3 dominant follicles. In another trial from The Netherlands, IUI with FSH and adherence to strict cancellation criteria had a low multiple pregnancy rate (1%) similar to CC (2%) [20]. Factors influencing conception Age has been identified as a significant predictor of conception [13, 21, 22, 23, 24]. In an Iranian cohort of women who underwent IUI for different etiologies, age 11 mm. As with earlier findings [13, 24, 25], our results do not allow us to classify endometrial thickness as a predictive factor of pregnancy. Studies on the optimal time interval between ovulation trigger and IUI have varied results but the Cochrane review published in 2014 found no difference in live birth rates between time frames ranging from 24 to 48 hours [26]. In a recent Chinese study, pregnancy rates were better when IUI was performed 24 hours post-trigger [27]. Ovulation occurring around the time of 67 the natural cycle was reported to positively affect the odds of pregnancy [11, 17, 27].

None of these factors affected the conception rate in our study. With respect to semen parameters, progressive motility and average total motile sperm count are predictors of IUI success [16, 22, 24]. Acceptable pregnancy rates were noted with postwash motile sperm count of at least 5 million by some [13, 17] while others

reported best rates with counts between 10 and 20 million [10] and >30 million [28]. We did not find any association when the count was analyzed as a continuous variable but IUI cycles performed with count >30 million had a significantly higher conception rate. It is obvious that there is a wide variation in the results reported by researchers with regard to conception rates and the factors potentiating / inhibiting successful IUI. Many of these conflicting observations stem from differences in treatment groups, diagnostic criteria, techniques used, age of the cohort, duration of infertility and the number of treatment cycles.

Strengths and limitations of the study
Strengths

Being a prospective study, the completeness of the data is a strong point of this study. All eligible patients fulfilling the inclusion and exclusion criteria were enrolled to avoid sampling bias. The relatively short study duration ensured uniformity in management as there were no changes in OS protocols or IUI procedure during these 18 months. The use of multiple cycles from a given patient in an analysis might lead to a lack of independence of data and the variables of non-pregnant subjects in multiple cycles are considered repetitively, each with the same weight as a variable from a single cycle of a pregnant patient which can lead to inaccurate 68 estimation of the importance of a single variable and its predictive value. To overcome this, the predictors were analyzed separately for the first IUI cycle.

Limitations

The sample size was calculated based on the primary outcome of pregnancy rate per cycle and was insufficient for a valid analysis of secondary outcomes. Despite the recruitment of all eligible women with unexplained infertility during the study period, the study was not adequately powered to carry out further intra-group analyses such as conception rates with different OS regimes. There was considerable heterogeneity with respect to the number of treatment cycles per couple, variation in the drugs used for OS and different starting doses for medicines which could have influenced the outcomes. Follow up of pregnancies and live birth rates could not be ascertained in all cases in the given time frame.

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Conflict of Interest
None

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