

Younger Women with Ovulation Disorders and Unexplained Infertility Predict a Higher Success Rate in Superovulation (SO) Intrauterine Insemination (IUI)

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Abstract

Introduction: Superovulation-intrauterine insemination (SO-IUI) is the most common assisted reproductive technique (ART) in the world, with good evidence of efficacy and cost-effectiveness. However, parameters affecting its success have not been consistently reported. So in this study, we aim at determining the parameters influencing the success rate of SO-IUI. **Materials and Methods:** We conducted a retrospective cohort study of 797 SO-IUI cycles from 606 patients, performed between 2007 and 2009 in a single centre. These women received clomiphene citrate (CC), recombinant FSH (rFSH) or both. **Results:** There were 127 clinical pregnancies with a pregnancy rate (PR) of 15.9% (127/797) per treatment cycle. Factors associated with higher PR included maternal age <38 ($P=0.02$), subfertility diagnoses of ovulatory disorders, unexplained infertility, sexual dysfunction and unilateral tubal obstruction ($P=0.02$), an endometrial thickness ≥ 8 mm ($P=0.03$), total number motile spermatozoa (TNMS) of ≥ 1 million ($P=0.03$), and spermatozoa normal forms (NF) $\geq 4\%$ ($P<0.01$) on bivariate analysis. When CC is used, the endometrial thickness is more likely to be suboptimal (<8 mm). All the above parameters remained significant except the subfertility diagnoses on multivariate analysis. **Conclusion:** Patients' selection with women <38 years old and preferably with ovulation disorders and unexplained infertility is associated with the highest PR in SO-IUI. Cycle parameters such as the use of rFSH alone, with the avoidance of CC, TNMS ≥ 1 million and NF $\geq 4\%$ is likely to result in the best outcomes and reduce the high order multiple pregnancy risk.

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Key words: Assisted reproductive technique, Fertility, Ovulation disorder, Predictive factors

Introduction

Intrauterine insemination (IUI) with or without stimulation is the most common assisted reproductive technique (ART) in the world. Currently, IUI is widely used for treating infertility as a cheaper, simpler and less invasive method compared to in vitro fertilisation (IVF) techniques. While there is good evidence of the efficacy and cost-effectiveness of stimulated IUI (SO-IUI),¹ the pregnancy rates (PR) of an unselected infertile population following homologous SO-IUI can vary from 8.2% to 16.9%.¹⁻⁶ Accordingly, the ESHRE Capri Workshop Group attempted, to clarify the role of individual parameters such as maternal age, aetiology of infertility, the ovulation induction drug utilised,

number of preovulatory follicles available and semen parameters. However, the results were either conflicting or non-informative.⁷ Thus, we conducted a retrospective study in a cohort of Southeast Asian patients undergoing SO-IUI in our centre with the aim of examining factors that influence the PR.

Materials and Methods

This is a single centre cohort study. Out of 907 treatment cycles started between 2007 and 2009, we excluded cycles which were not stimulated, cancelled due to under- or over-

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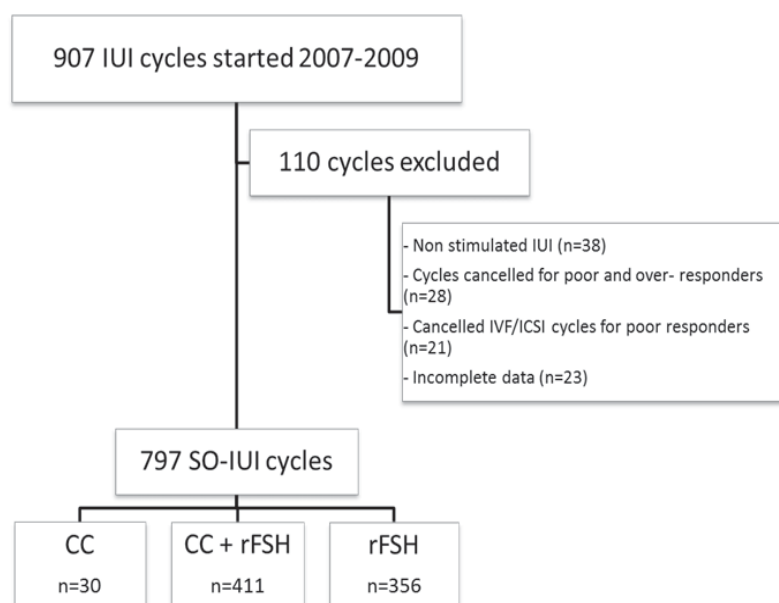


Fig. 1. Study flowchart.

response, and those where data were incomplete (Fig. 1). Only homologous cycles using patient's spermatozoa were included. The primary outcome was a clinical pregnancy, where a fetal cardiac activity is seen at 6 weeks of amenorrhea. The other parameters analysed were maternal age, aetiology of infertility, type of stimulation, number of mature follicles achieved, spermatozoa normal forms (NF) and total number of motile spermatozoa (TNMS) inseminated. This study was approved by the Institutional Review Board.

Ovarian stimulation was initiated on Day 2 of the menstrual cycle with either clomiphene citrate (CC), recombinant follicle stimulating hormone (rFSH) (Puregon, Organon, France) or a combination of CC and rFSH. CC was given at 50 mg per day from Day 2 to 6 of the menstrual cycle, while rFSH was given either from Day 7 in a mixed cycle with CC, or from Day 2 in a rFSH-alone cycle (50 to 75 IU), and the dose altered accordingly from Day 8 of stimulation.

Follicular sizes were determined by the average of the 2 maximum diameters measured by transvaginal ultrasound. Human chorionic gonadotropin (5000 units of Pregnyl, Organon, France) was administered when at least 1 mature follicle (≥ 16 mm) was achieved, followed by IUI 36 hours later in the absence of endogenous luteinizing hormone (LH) surge. When an endogenous LH surge has occurred with a mid-size follicle (14 to 16 mm), hCG was administered and the IUI performed 24 hours later. Cycles where the endogenous LH surge occurred where follicle size was < 14 mm were excluded.

Semen was processed by the swim-up method,⁸ concentrated with HTF medium (Irvine Scientific, USA) and supplemented with human serum albumin (Baxter, USA). Density and motility of the spermatozoa were assessed following WHO criteria⁸ and morphology following strict Kruger criteria.⁹ IUI was done with a Tomcat catheter (Cottman SBA, Australia). Luteal phase support through 400 mg cyclogest pessaries for 17 days post IUI were given for the rFSH-alone group only (Dumex-AlphaApS, Denmark), and clinical pregnancies determined at 6 weeks of amenorrhea.

Statistical Analysis

Bivariate association between clinical pregnancy and baseline characteristics of patients such as age, body mass index (BMI), parity, basal early follicular serum FSH and subfertility diagnosis were evaluated using the Fisher's exact test. To take into account the possible intrasubject correlation in outcome where multiple cycles were involved, the mixed effect logistic regression model was used to evaluate the effect of risk factors such as number of mature follicles ≥ 16 mm, endometrial thickness, stimulation protocol, TNMS and NF.

Significant risk factors in the bivariate analyses were further considered for inclusion in the multivariable mixed-effects logistic regression model to identify predictors of clinical pregnancy. The variable selection was made via the likelihood ratio test. All statistical analyses were generated using STATA v.12, assuming a 2-sided test at the 5% level of significance.

Results

A total of 907 cycles were started during the study period, of which 797 cycles from 606 patients were analysed after excluding non-stimulated cycles ($n = 38$), cancelled cycles from under and over-responders ($n = 28$), cancelled IVF cycles ($n = 21$), and where data was incomplete ($n = 23$) (Fig. 1). Fifty-seven percent were ethnic Chinese, 25% were Indians, 7% were Malays and 10% were composed of Caucasians and others, reflecting a typical South East Asian population (Table 1).

Seventy-two percent of the patients were aged below 35 years, 17% of them were between 35 and 38 years and 11% of them were 38 years and above. Sixty-seven percent had normal body mass index (BMI), with 24% being overweight and 9% obese. Eighty-one percent are nulligest and 96% of them have a normal ovarian reserve (Day 2/3 FSH <10 mIU/L). The most prevalent subfertility diagnoses were male factor (35%), combination of male factor and ovulatory disorder (23%), and multiple factors (21%). Seventy-two percent of patients had undergone a single cycle, 24% and

Table 1. Characteristics of 606 Patients Undergoing SO-IUI and Bivariate Analysis of Clinical Pregnancy Rates (PR) According to Patients' Characteristics

Patients' Characteristics	n	%	PR	OR (95% CI)	P value
Age (years)					0.022
<35	434	71.6	21.4	1.00	
35 to <38	105	17.3	20.0	0.92 (0.51 – 1.59)	
38 to <40	40	6.6	5.0	0.19 (0.02 – 0.77)	
≥ 40	27	4.5	7.4	0.29 (0.03 – 1.22)	
Ethnicity					0.203
Chinese	349	57.6	20.3	1.00	
Malay	40	6.6	15.0	0.69 (0.23 – 1.75)	
Indian	152	25.1	19.1	0.92 (0.55 – 1.53)	
Caucasian	5	0.8	60.0	5.87 (0.66 – 71.1)	
Others	60	9.9	15.0	0.69 (0.29 – 1.51)	
BMI (kg/m²)					0.825
<25	344	66.5	19.8	1.00	
25 to <30	125	24.2	17.6	0.87 (0.48 – 1.51)	
≥ 30	48	9.3	20.8	1.07 (0.45 – 2.32)	
Parity (live birth)					0.581
0	456	81.4	18.6	1.00	
≥ 1	104	18.6	21.2	1.17 (0.66 – 2.02)	
FSH_{D2-3} – mIU/L					0.099
<10	536	95.9	19.8	1.00	
≥ 10	23	4.1	4.3	0.18 (0.01 – 1.17)	
Subfertility diagnosis					0.021
Male factor	210	34.7	17.1	1.00	
Ovulatory disorders	44	7.3	31.8	2.26 (1.00 – 4.90)	
Male factor + Ovulatory disorders	137	22.6	19.7	1.19 (0.65 – 2.13)	
Tubal factor	8	1.3	25.0	1.61 (0.15 – 9.46)	
Ovarian failure	8	1.3	12.5	0.69 (0.01 – 5.66)	
Sexual dysfunction	6	0.99	66.7	9.67 (1.31 – 108.91)	
Unexplained	56	9.2	26.8	1.77 (0.82 – 3.68)	
Multiple factors	126	20.8	13.5	0.75 (0.38 – 1.46)	
Others	11	1.8	18.2	1.07 (0.11 – 5.51)	

Note: Bivariate analysis based on mixed effects logistic regression model

BMI: Body Mass Index

3% proceeded to 2 or more cycles respectively. A total of 127 pregnancies were achieved over 797 cycles (PR = 15.9% per cycle). In this bivariate analysis, the highest PR was achieved within the second cycle with a PR of 12.9% (78/606) compared to 9.7% (16/169) and 9.4% (2/22) respectively in cycle 1 and 3, although the results did not reach statistical significance ($P = 0.53$) possibly due to the small numbers involved (Table 2). Of the 127 patients with clinical pregnancy, 14 (11.0%) had a multiple pregnancy, of which 4 (3.1%) were high-order multiple pregnancies.

Patients younger than 35 years old have a 4-fold higher chance in conceiving compared to those 38 years or older, while ethnicity, BMI, parity and baseline FSH levels had no significant impact on PR. The bivariate analysis also showed subfertility diagnosis to be a predictive factor for clinical pregnancy ($P = 0.02$), with diagnoses of sexual dysfunction, ovulation disorder and unexplained infertility resulting in better PR compared to other diagnoses (Tables 1 and 2).

A mono-follicular response (single follicle of ≥ 16 mm diameter) was seen in 54% of cycles, while multi-follicular responses (2 follicle or ≥ 3 follicles recruited), were represented in 25% and 7% of the cycles respectively. There was a trend towards an increase in the PR with increasing number of mature follicles, from a PR of 10.3% with a single follicle ≥ 16 mm in diameter, to 15.5% for 3 or more follicles ($P = 0.3$). Even in cycles where no mature follicle was observed (14%), the PR achieved was 8.6%. In this particular group of patients contributing to 112 cycles, at least one mid-size follicle (14 to 16 mm) was observed in 91% of cycles (102/112), with a PR of 10.8% ($n = 11/102$). There were no pregnancies achieved where all follicles were < 14 mm diameter. Endometrial thickness ≥ 8 mm at the time of hCG trigger was associated with a higher PR compared with < 7 mm (OR 3.01, 95% CI 1.10 to 8.23, $P = 0.03$). An endometrial thickness of ≥ 8 mm was achieved in 3%, 41% and 56% of CC, CC+rFSH and rFSH alone groups respectively.

Table 2. Bivariate Analysis of Clinical Pregnancy Rate (PR) According to Cycle Parameters

Cycle Parameters	N Cycles	PR (%)	OR (95% CI)	P value
Number of mature follicle ≥ 16 mm				0.303
0	112	8.6	1.00	-
1	429	10.3	1.22 (0.60 – 2.51)	0.582
2	198	14.2	1.78 (0.82 – 3.86)	0.147
≥ 3	57	15.5	1.95 (0.72 – 5.32)	0.190
Endometrial thickness (mm)				0.090
< 7	84	4.2	1.00	-
7	133	9.2	2.33 (0.77 – 7.09)	0.135
≥ 8	576	11.6	3.01 (1.10 – 8.23)	0.032
Stimulation protocol				0.548
Clomid	30	6.3	1.00	-
Clomid + rFSH	411	10.3	1.71 (0.41 – 7.16)	0.460
rFSH	356	11.9	2.03 (0.48 – 8.55)	0.336
TNMS (millions)				
< 1	42	1.0	1.00	-
≥ 1	753	11.2	12.19 (1.36 – 109.54)	0.026
NF (millions) before preparation				
< 4	507	9.2	1.00	-
≥ 4	289	16.2	1.90 (1.20 – 3.00)	0.006
Number of cycles				0.527
1	606	9.7	1.00	-
2	169	12.9	1.38 (0.78 – 2.42)	0.262
≥ 3	22	9.4	0.96 (0.24 – 3.75)	0.949

Note: Bivariate analysis based on mixed effects logistic regression model.

NF: Normal forms; rFSH: Recombinant follicle stimulating hormone; TNMS: Total number motile spermatozoa

In terms of the modality of superovulation, rFSH alone yielded a higher PR of 11.9% ($n = 356$ cycles) as compared to 10.3% when combined with CC ($n = 411$) and 6.3% for CC ($n = 30$) alone, although results were not statistically significant. Of the 14 patients with multiple pregnancies, 10 received CC+rFSH ($n = 10/411$, 2.4%), while the other 4 received rFSH only ($n = 4/356$, 1.1%). All four cases of higher order multiple pregnancies occurred in the CC+rFSH group. PR was significantly higher when TNMS was ≥ 1 million (11.2% vs 1.0%, $P = 0.03$) and NF $\geq 4\%$ (16.2% vs 9.2%, $P < 0.01$).

The following variables which were significant at the 10% level in the bivariate analysis were further considered for inclusion in the multivariable mixed effect logistic regression model, taking into account the effects of potential confounders: age, subfertility diagnosis, basal early follicular serum FSH, endometrial thickness, TNMS and NF. Based on the likelihood ratio test, only age, TNMS, endometrial thickness and NF were eventually found to be important predictors of clinical pregnancy outcome (Table 3). Consistent with the bivariate analysis, the odds of clinical pregnancy were reduced for women between 38 and 40 years (adjusted OR = 0.18, 95% CI, 0.03 to 0.97, $P < 0.05$) and above 40 years (adjusted OR = 0.21, 95% CI, 0.04 to 1.18, $P = 0.076$). Conversely, endometrial thickness of at least 8 mm conferred a beneficial effect on PR (adjusted

OR = 3.13; 95% CI, 1.13 to 8.69, $P = 0.03$) as did TNMS ≥ 1 million (adjusted OR = 9.96; 95% CI, 1.07 to 92.55, $P < 0.05$) and NF $\geq 4\%$ (adjusted OR = 1.88, 95% CI, 1.13 to 3.11, $P = 0.02$). A multivariable mixed-effects logistic regression model involving age, endometrial thickness, TNMS and NF did not improve on the predictive value (AUC 0.6439).

Discussion

Over the past decade, success rates with IVF treatment has improved substantially, with live-birth rates reaching more than 30% in Europe and North America.^{1,10} In this context, the role of SO-IUI has to be redefined. In particular, the critical factors governing success rates needs to be determined to better select the group of patients who can benefit the most from it. Until now, there is only but one published study in an Asian population for IUI, but not for stimulated IUI.¹¹ Our retrospective analysis of 606 Asian couples who had undergone 797 SO-IUI cycles over a period of 3 years resulted in an overall PR of 15.9% per cycle. This is comparable to other published studies reporting PR between 8.2% and 16.9%.^{2,4-6}

In our study, the woman's age was a strong predictor of success with an almost 4-fold higher pregnancy rates achieved in women younger than 38 years old, as reported by several other groups.^{2,4,6,12-14}

The most prevalent diagnoses in our cohort were isolated male factor, a combination of male factor and ovulation disorder and multiple factors. In our study, we had 6 couples suffering from sexual dysfunction, with 4 of them conceiving (PR = 67%). Only one article from Denil and colleagues in 1996, described the outcome of SO-IUI and IVF/ICSI cycles in young adults ($n = 37$) suffering from ejaculatory disorders, where PR of 14% per IVF cycle was achieved, with no success noted with the use of SO-IUI.¹⁵ We obtained good PR with ovulation disorders and unexplained infertility (PR of 32% and 27% respectively), which is similar to the 33% PR reported by Guzick and colleagues' randomised controlled trial on SO-IUI in a population of unexplained infertility.¹⁶

We observed a trend towards an improved PR with increasing number of mature follicles, in keeping with the reports from a few other groups,^{3,5,17} although there had been other groups which did not demonstrate this correlation.¹⁸⁻²⁰ This could be due to the differences in defining the size of a mature follicle. Both Steures and Merviel have used a follicular size of ≥ 16 mm,^{2,13} while others have defined it as ≥ 18 mm.^{3,5} Although there is no definitive study on what constitutes a mature follicle, study by Gleicher et al on 3347 SO-IUI cycles concluded that the number of follicles 16 mm or larger was not significantly associated with the

Table 3. Predictors of Clinical Pregnancy Outcome

Characteristics/Cycle Parameters	Adjusted OR (95% CI)	P value
Age (years)		0.02
<35	1.00	-
35 to <38	1.07 (0.56 – 2.03)	0.834
38 to <40	0.18 (0.03 – 0.97)	0.045
≥ 40	0.21 (0.04 – 1.18)	0.076
Endometrial thickness (mm)		0.038
<7	1.00	-
7	2.25 (0.74 – 6.88)	0.155
≥ 8	3.13 (1.13 – 8.69)	0.028
TNMS (millions)		
<1	1.00	-
≥ 1	9.96 (1.07 – 92.55)	0.043
NF (millions) before preparation		
<4	1.00	-
≥ 4	1.88 (1.13 – 3.11)	0.015

Note: Multivariate mixed-effects logistic regression model
NF: Normal forms; TNMS: Total number motile spermatozoa

incidence of pregnancy neither with high-order multiple pregnancy while the total number of follicles was.²¹ This was later confirmed by Tur et al, in a large series of 1878 consecutive pregnancies demonstrating that the number of growing follicle (≥ 10 mm) on the day of hCG was a better predictor of high-order multiple implantation than the number of mature follicles.²² These studies suggest that, besides the number of mature follicles, the total number of follicles in the cohort, especially the mid-size ones, is correlated with the risk of high-order multiple pregnancies. In our cohort, pregnancies were also observed in the absence of a mature follicle, although all of them have at least one mid-sized (14 to 16 mm diameter) follicle.

In spite of similar PR in the CC-rFSH and rFSH treatment groups, we observed a 2-fold higher multiple pregnancy rates in the CC-rFSH group, with all 4 higher order pregnancies (triplets) occurring in this group. However, because of the small number of the CC group ($n = 30$), its outcome cannot be meaningfully compared to the other 2 stimulation protocols.

The probability of achieving a pregnancy for an endometrial thickness ≥ 8 mm was thrice that of those < 7 mm. We find that the addition of CC into the superovulation protocol (CC alone and CC-rFSH) had a detrimental effect on the endometrium results with an 18-fold increase in the likelihood of having an endometrial thickness (ET) ($ET < 7$ mm in 18.4% versus 0.8% in the rFSH group). This was in keeping with findings by Dickey et al in 474 SO-IUI cycles.²³

Patients with normal sperm morphologies ($NF \geq 4\%$) had a 2-fold higher PR in our cohort. This was similar to van Waart et al's meta-analysis of 6 SO-IUI studies.²⁴ However, Wainer et al failed to find a correlation between morphology and pregnancies.²⁵ This could be due to the differences in the method employed, and the evolving cut-off values over the past few decades.^{8,26-29} With respect to the TNMS, the probability of conceiving was 11-fold higher when TNMS was 1 million and above, in broad agreement with most published studies.^{4,5,30}

Conclusion

In this first study of SO-IUI in an Asian population, we have shown that SO-IUI is most effective in women < 38 years old, when the indication is sexual dysfunction, unexplained infertility, ovulation disorder, when the endometrial thickness ≥ 8 mm, when TNMS is at least 1 million and the normal morphology $\geq 4\%$. To optimise the success rate and reduce the high order multiple pregnancy risk, the use of rFSH alone, with the avoidance of CC is likely to result in the best outcomes. Furthermore, both the number of mid-size and mature follicles should be monitored closely to avoid higher order multiple pregnancies.

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