ORIGINAL ARTICLE

Prognostic Factors Influencing Pregnancy Rate after Stimulated Intrauterine Insemination

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SUMMARY

To determine the prognostic factors such as age, diagnosis, number of cycle attempts and semen parameters on the pregnancy rate of controlled ovarian hyperstimulation (COH) /intrauterine insemination (IUI). Three hundred and seventeen women who underwent 507 consecutive COH/IUI cycles were recruited from 1st January 2002 to 31st December 2005 inclusively. This retrospective study was done in University Malaya Medical Centre, a tertiary care academic centre. The main outcome measure was pregnancy rate according to age, infertility diagnosis, duration of infertility, semen parameters, and the number of treatment cycles. The overall pregnancy rates were 16.9% per cycle and 25.9% per couple. Pregnancy rates decreased with advancing maternal age. Pregnancy rate was also significantly lower in patient with postwash total motile sperm count (TMSC) ≤20 million/ml compared to those with TMSC >20 million/ml. The cumulative pregnancy rates varied greatly by diagnosis from 16% for patients with male factor infertility to 60% for patients with ovulatory disorder. Pregnancies among patients with male infertility, tubal factors infertility and endometriosis were achieved during the first three cycles. There is a clear age-related decline in fecundity associated with COH/IUI treatment. Women of >40 years old, couple with postwash TMSC ≤20 million/ml, severe endometriosis and tubal factors have a particularly poor prognosis.

KEY WORDS:
Intrauterine insemination, Infertility, Pregnancy, Prognosis, Controlled ovarian hyperstimulation

INTRODUCTION

The effectiveness of ovulation induction and IUI in persistent infertility was the subject of a meta-analysis of 22 trials[1]. The investigator concluded that the average fecundability increased approximately five folds when controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI) were used, compared with an untreated cycle.

The reported pregnancy rates per COH/IUI cycle in different parts of the world usually varied between 7% and 22%[2, 3, 4, 5, 6]. The great variation in pregnancy rate achieved may be due to the small size of the study population, variability in characteristics of patients, ovarian stimulation protocol and insemination techniques. In Malaysia, data on the prognostic factors related to IUI treatment in which clomiphene citrate/gonadotrophin/human chorionic gonodotrophin (HCG) is used for ovarian stimulation is rare. There is also a lack of consensus regarding the optimum numbers of COH/IUI that patients should attempt before proceeding to in-vitro fertilisation.

In this study, we conducted a retrospective analysis on 507 consecutive COH/IUI cycles (using a combination of clomiphene citrate, gonadotrophin and HCG) over a 4-year period in a teaching hospital in Kuala Lumpur. Our aim is to analyze the influence of patient age, duration of infertility, infertility diagnosis, semen parameter, and number of treatment cycles on the cycle fecundity of women undergoing COH/IUI treatment as assessed by cumulative pregnancy rates. The findings of this analysis may provide a more rational basis for counseling patients about treatment options in our local setting.

MATERIALS AND METHODS

The medical records of 317 infertile couples who had undergone a total of 507 cycles with Clomiphene citrate/Gonadotrophin/HCG induced COH/IUI at the Reproductive Unit in University Malaya Medical Centre from 1st January 2002 to 31st December 2005 inclusively were reviewed retrospectively. All the patients were identified from the record log book in the infertility clinic.

All the couples must have at least one year duration of infertility. The pretreatment evaluation included a semen analysis, ovulation assessment by a mid-luteal progesterone level, hysterosalpingography (HSG) or hysteroscopy to assess the uterine cavity and demonstration of tubal patency by HSG or laparoscopy. Among women with a short duration of infertility (less than two years) or those women with intrauterine pregnancy in the immediate past and no history suggestive of tubo–peritoneal disease, examination of tubal patency was not always carried out before the first IUI treatment. However, tubal patency was investigated if pregnancy did not occur after 1-2 cycles of IUI.

A proforma was designed to record the age, parity, duration of infertility, aetiology, number of treatment cycles and partner's semen parameters. The couples were divided into two groups according to the age of the female partner: ≤40 years old (n = 474) and >40 years old (n = 33). The duration of infertility was divided into ≤ 6 years (n = 387) and >6 years (n = 120). There were 334 cases of primary infertility and 173 cases of

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secondary infertility in our series. The couples also were grouped according to their infertility diagnosis: mild male factor (defined as a semen analysis showing a concentration of <20x10^6/mL [World Health Organisation, WHO[7]] after the washing of the sperm and the absence of any pathology in the female partner) (n = 69); anovulation (n = 100) or severe endometriosis with ASRM score >15 [8], (n = 48), tubal factor (defined as any abnormality of one or both fallopian tubes or a history of any tubal surgery) (n = 92); and unexplained infertility (defined as the absence of identifiable pathology [i.e., a normal semen analysis, documentation of ovulation, a normal uterine cavity, patent fallopian tubes, and the absence of peritoneal pathology]) (n = 198).

For statistical comparison, intrauterine insemination pregnancy rate was stratified according to post-wash sperm parameters. Total motile sperm count (TMSC) were derived from total sperm count multiply by percentage of motile sperm (Grade A, B and C). The post-washed TMSC were divided into ≤20 million/ml (n = 73) and >20 million/ml (n = 434).

Ovarian stimulation
All women in the study underwent ovarian stimulation using clomiphene citrate and gonadotropins (Gonal F, Serono, Aubonne, Switzerland or Puregon, Oss, Netherland). The patient were prescribed 100 to 150 mg of clomiphene citrate starting on day 2 to 6 of the cycle, followed by 1 to 2 ampoules of gonadotropins daily. Ovarian and endometrial responses were monitored by vaginal ultrasonography on day 9 to 13. Human Chorionic Gonadotropin (5,000 IU Pregnyl, Organon) was given when the leading follicle reached pre-ovulatory size at diameter of at least 18 mm. Standard IUI was performed 36 h after administration of HCG. Utrogestan 200mg vaginal pessaries were prescribed twice daily following IUI for duration of two weeks.

Sperm Preparation/Washing
Semen was collected by masturbation into a sterile bottle after 2–4 days of sexual abstinence. The standard swim-up techniques was used for preparation, employing Sil-Select Plus culture medium (FertoPro N.V., 8730 Beernem, Belgium). The sperm sample is layered below the washing medium and left for 45 minutes. The top layer (which now contained the most active sperm) is drawn up to 0.5 to 1 ml with a clean syringe and then centrifuge at 1800rpm for 5 minutes. The supernatant was discarded leaving 0.5ml for insemination.

Intrauterine insemination
Intrauterine insemination was performed using an intrauterine catheter (Genetics IUI catheter, Belgium) attached to a 2-ml syringe. The catheter was gently passed through the cervical canal and the sperm suspension expelled into the uterine cavity. Insemination volumes ranged from 0.5 to 2 ml. The women remained supine for 30 - 40 min after IUI. If menstruation was delayed, plasma HCG was measured. All pregnancies were confirmed by ultrasonography.

Statistical analysis
All data were recorded in SPSS version 11.0 and the proportional data were analyzed using X^2 test. *P value* < 0.05 is considered to be of statistical significance. The probability of success after COH/IUI was estimated with the use of Kaplan-Meier life table analysis stratified by the infertility diagnosis and number of treatment cycles.

RESULTS
A total of 507 IUI cycles were analyzed. The overall pregnancy rate per cycle and per couple was 16.2% (82/507) and 25.9% (82/317) respectively. Pregnancy outcome is presented in Table I. The median female age and duration of infertility was 33±2.1 (range 22-47) years and 5±4.3 (range 1 – 16) years, respectively.

The pregnancy rates stratified according to the female characteristics and sperm parameters before and after preparation were summarized in Table II. The pregnancy rate in women ≤40 years old was significantly higher than those >40 years old (P < 0.05). Out of the 33 women > 40 years old, only two pregnancies were achieved. Women with infertility duration of ≤ 6 years were associated with a better pregnancy rate compared with duration of infertility > 6 years (15.2% and 10.2% respectively). However this was not statistically significant. Primary and secondary infertility did not significantly affect the outcome of IUI treatment. In our series, couples with post-wash TMSC ≤20 million/ml achieved a significantly lower pregnancy rate when compared with those couple with post wash TMSC >20 million/ml (2.7 versus 18.4% respectively, p < 0.01).

Regarding the diagnosis of infertility, women with unexplained infertility and anovulation have higher pregnancy rates (18.6% and 22% respectively) in compared to women suffering from severe endometriosis (7.1%), male factor (11.5%) or tubal factor (10.8%) (Table II).

The life table analysis was performed to assess the correlation among the fecundity rate, infertility diagnosis and treatment cycle number (Figure 1). The cumulative pregnancy rates by diagnosis were highest among patients with ovulatory factor as well as unexplained infertility (60% and 51% respectively). The cumulative pregnancy rates were 13% for patients with male factor infertility, 28% for patients with endometriosis, and 18% for patients with tubal factor infertility. All pregnancies among patients with male factor infertility, tubal factor infertility and endometriosis groups were achieved during the first three treatment cycles.

DISCUSSION
The objectives of this retrospective study were to evaluate the overall pregnancy rate in a general infertility practice following COH/IUI and to identify any prognostic factors that would predict the pregnancy outcome. In our study, it has demonstrated a decline in cycle fecundity with increasing female age. In addition, patients with ovulatory disorders and unexplained infertility had the best prognosis for pregnancy after IUI treatment. The vast majority of pregnancies occurred during the first three treatment cycles.

Overall fecundity rates for patients undergoing COH/IUI with gonadotropins have varied from 7% to 29% [2, 3, 4, 5, 6]. The overall fecundity for all treatment cycles in our study was 16%. The pregnancy rates following IUI treatment were stratified according to the different etiological groups,

Table I: Pregnancy outcome of the controlled ovarian stimulation (COH) /intrauterine insemination (IUI) cycles over a 4-year period. Values in parentheses are percentages.

Pregnancy outcome	No. of patients (%)
Pregnancies/cycle	82/507 (16.1)
Pregnancies/couple	82/317 (25.9)
Live births	66/82 (80.4)
Miscarriages	11/82 (13.4)
Ectopic pregnancies	5/82 (4.8)
Multiple pregnancy	6/82 (7.3)

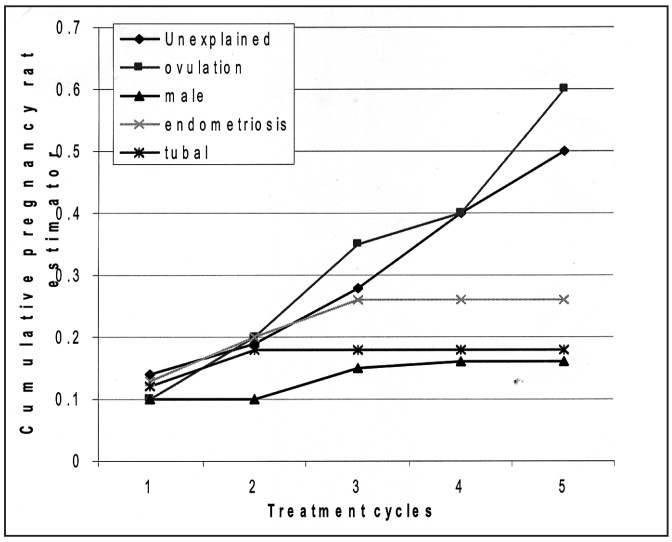

Fig. 1: The cumulative pregnancy rates according to the number of treatment cycles.

ovarian dysfunction (22%), unexplained infertility (18.6%), male factor infertility (11.5%), tubal infertility (10.8%) and endometriosis (7.1%). Our results are generally in agreement with prior studies.

The prognostic value of the woman's age was not considered to be significant in several studies[9, 10]. However, Frederick *et al.* [11] found that success with IUI was reduced significantly in women aged >40 years. The prognosis can be refined further with the addition of an early follicular phase FSH level[12] or a clomiphene citrate challenge test[13]. Legro *et al* also observed that, the clinical pregnancy rate (PR) per cycle in women aged 40 – 43 undergoing COH/IUI was 5.2% and only one pregnancy occurred in six cycles in women above age 44[14]. In our study, there was a significantly lower pregnancy rate in women aged >40 years old, with only two pregnancies reported among 33 patients.

Normal semen quality is usually verified using the World Health Organization (WHO) criteria, but these criteria have little prognostic value in IUI, as pregnancy rates with IUI are acceptable even with semen below the WHO thresholds for normal semen quality[15, 16]. In view of these data, the post-wash total motile sperm count (TMSC) has been proposed as a test to distinguish the couples who would benefit from IUI from the couples who would benefit more from IVF or ICSI[17, 18]. The post-wash TMSC represents the total number of motile sperm that are present after preparation and are subsequently available for insemination in IUI. This TMSC may be assessed during the fertility workup or at the actual time of insemination.

Table II: Intrauterine insemination pregnancy rate according to female characteristics and post wash total motile sperm count (TMSC) parameters

	Pregnancies/cycle (%)
≤40 years old	80/474 (16.9)
>40 years old	2/33 (6.1)*
≤6 years of infertility	69/387 (17.8)
>6 years of infertility	13/120 (10.8)
Unexplained	37/198 (18.6)
Ovarian dysfunction	22/100 (22.0)
Male factor	8/69 (11.5)
Endometriosis	5/48 (7.1)
Tubal Factor	10/92 (10.8)
Primary infertility	47/334 (14.0)
Secondary infertility	35/173 (20.2)
TMSC ≤20x10^6/ml	2/73 (2.7) †
TMSC >20x10^6/ml	80/434 (18.4)

*P <0.05 † P <0.01

The predictive value of post-wash TMSC on the IUI outcome was the subject of a meta-analysis of 16 trials[19]. The investigators concluded that an optimal cut-off value for the post-wash TMSC at insemination to use for patient counseling could not be identified. The authors agreed that as long as there are no data on the subject, the cut-off value for a post-wash TMSC during the fertility workup should be based on the clinic's own population and sperm-preparation technique. In the literature, the proposed cut-off values below which the IUI is not advised ranged between 0.3 and [20] million post-wash progressively motile spermatozoa[15, 17, 18, 20]. In our study, the pregnancy rate following IUI was rather discouraging when the post-wash TMSC <20 million/ml.

In our study, nearly 98% of all the patients who conceived did so during the first three cycles. For patients with ovulatory disorders or unexplained infertility, the prognosis remains good for up to six treatment cycles. Because of the poor prognosis for pregnancy in infertile women >40 years of age and those with stage III and IV endometriosis, one should question the cost-effectiveness of performing the COH/IUI and perhaps these 'older' patients should consider IVF as the first line of treatment. The number of treatment cycles also should be limited for patients with male factor infertility and tubal factor infertility, who have a particularly poor prognosis in the COH/IUI treatment. These groups of patients should be moved rapidly from the COH/IUI to a more aggressive treatment such as IVF.

The principal weaknesses of this study, in addition to the fact that it is a retrospective cohort study and not randomized, are the low number of patients who received more than four cycles of CC-IUI, and the high dropout rate per cycle. The former was related in part to an effort by the physicians to follow an algorithm of three cycles of COH-IUI before IVF. When this was not followed, it was principally because the patient could not afford or unwilling to undergo a more aggressive treatment. In addition, retrospective study often carries an element of bias as the clinicians discouraged the patients with a poor prognosis from continuing with the treatment and encouraged those who could better benefit from IVF to attempt for that treatment earlier.

Likewise, dropouts were principally due to the above reasons plus dissatisfaction with the need for cycle monitoring or injections and frustration for not becoming pregnant. Dropouts as a result of poor response were rare in this analysis of patients who had to develop preovulatory follicles to receive hCG and IUI. Dropouts are a common problem in studies of infertility patients as they need to pay for part or all of their treatment [21, 22]. Land *et al.* [22] determined the reasons for dropouts in an IVF program where treatment was free for the first three cycles. After the first and second cycles, the dropout rate was 26%, of which 33% was because of poor prognosis. Dropouts increased to 66% after the third cycle when the patients would have to pay for further treatment.

In conclusion, our study seeks to address the pragmatic problem of identifying prognostic factors that influence the pregnancy outcome following COH/IUI treatment. Favorable prognostic factors for treatment success following stimulated IUI treatment are women aged <40 years, infertility causes such as anovulation and unexplained infertility, post-washed TMSC of >20 million/ml. This information is helpful in counseling the subfertile couples entering the infertility treatment, and makes it possible to carry out more precise patient selection and thereby further increases the cost-effectiveness of IUI therapy.

REFERENCES

1. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod 1997; 12: 1865-72.
2. Houmard BS, Houmard M, Peter J, *et al*. Factors influencing pregnancy rates with a combined clomiphene citrate/gonadotropin protocol for non-assisted reproductive technology fertility treatment. Fertil Steril 2002; 77: 384-86.
3. Richard P, Taylor SN, Lu P, Sartor BM, Pyrzak R. Clomiphene citrate intrauterine insemination (IUI) before gonadotropin IUI affects the pregnancy rate and the rate of high-order multiple pregnancies. Fertil Steril 2004; 81: 345-48.
4. Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril 2006; 86: 566-71.
5. Dmowski WP, Pry M, Ding J, Rana N. Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation–intrauterine insemination or in vitro fertilization–embryo transfer. Fertil Steril 2002; 78: 750-56.
6. Steures P, van der Steeg JW. Prediction of an ongoing pregnancy after intrauterine insemination. Fertil Steril 2004; 82: 45-51.
7. World Health Organization. Laboratory manual for the examination of human semen and semen-cervical mucus interaction. 3rd ed. New York: Cambridge University Press, 1992; 1-25.
8. American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis. Fertil Steril 1997; 67: 817-21.
9. Brzechffa PR, Buyalos RP. Female and male partner age and menotrophin requirements influence pregnancy rates with human menopausal gonadotropin therapy in combination with intrauterine insemination. Hum Reprod 1997; 12: 29-33.
10. Tomlinson MJ, Amissah-Arthur JB, Thompson KA, Kasraie JL, Bentick B. Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. Hum Reprod 1996; 11: 1892- 6.
11. Frederick JL, Denker MS, Rojas M *et al*. Is there a role for ovarian stimulation and intra-uterine insemination after age 40? Hum Reprod 1994; 9: 2284-96.
12. Toner JP, Philput CB, Jones GS, Muasher SJU. Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age. Fertil Steril 1991; 55: 784 -91.
13. Scott RT, Hofmann GE. Prognostic assessment of ovarian reserve. Fertil Steril 1995; 63: 1-11.
14. Legro RS, Shackleford DP, Moessner JM, *et al*. ART in women 40 and over. Is the cost worth it? J Reprod Med 1997; 42: 76-82.
15. Branigan EF, Estes MA, Muller CH. Advanced semen analysis: a simple screening test to predict intrauterine insemination success. Fertil Steril 1999; 71: 547-51.
16. Dickey RP, Pyrzak R, Lu PY, Taylor SN, Rye PH. Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal sperm. Fertil Steril 1999; 71: 684-9.
17. Arny M, Quagliarello J. Semen quality before and after processing by a swim-up method: relationship to outcome of intrauterine insemination. Fertil Steril 1987; 48: 643-8.
18. Francavilla F, Romano R, Santucci R, Poccia G. Effect of sperm morphology and motile sperm count on outcome of intrauterine insemination in oligozoospermia and/or asthenozoospermia. Fertil Steril 1990; 53: 892-7.
19. van Weert JM, Repping S, Van Voorhis BJ, *et al*. Performance of the postwash total motile sperm count as a predictor of pregnancy at the time of intrauterine insemination: a meta-analysis. Fertil Steril 2004; 82: 612-21.
20. Berg U, Brucker C, Berg FD. Effect of motile sperm count after swim-up on outcome of intrauterine insemination. Fertil Steril; 1997; 67: 747-50.
21. Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. N Engl J Med 2000; 343: 2-7.
22. Land JA, Courtar DA, Evers JLH. Patient dropout in an assisted reproductive technology program: implications for pregnancy rates. Fertil Steril 1997; 68: 278-81.