Predictors of Intrauterine Insemination Success

M R R Zainul, DM*, F B Ong, Ph.D, M H Omar, MOG, S P Ng, MOG*, A Nurshaireen, BSc.*, M D Rahimah, Dip.MLT, S Mariam, Dip.MLT*, M Zolaidah, BSc., N S M N Sharifah-Teh, BSc., A Saniros, Dip.Nursing, B Hasnita, Dip.Nursing

*Department of O&G, **Department of O&G, Medical Faculty, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur

Summary

Intrauterine insemination (IUI) remains a therapeutic option within means of the majority of infertile couples in Malaysia. Therefore additional information on predictors of IUI success in the local context would provide a more concrete basis for counseling patients on expectations and treatment options. A retrospective analysis of 297 couples who underwent 445 IUI cycles from Jan 2005-Mar 2006 was undertaken. Four fifths were Malay with a mean paternal and maternal age of 35.53±5.82 (range 24-59) and 33.02±4.69 (range 21-46) years respectively. Causes of infertility were idiopathic (50%), endometriosis (17%) and anovulation/polycystic ovarian syndrome (15%). Almost 10% were oligoastenoteratozoospermic with another 23% oligozoospermic or astenozoospermic. Combined male and female factors occurred in 26%. A pregnancy rate (PR) of 9.4% per cycle; 14.1% per couple with a cumulative PR of 36.7% per 4 cycles was achieved. Those who became pregnant were significantly younger (31.29±4.43 vs. 33.21±4.68 years, p=0.011) and had more follicles (13.95±9.72 vs. 11.43±6.67, p=0.029) at the time of insemination. PR depreciated with maternal age and semen quality. Maternal and paternal age was inversely correlated to the number of follicles recruited (r=-0.30, p<0.0005) and progressive sperm motility (r=-0.125, p=0.013) respectively.

Key Words: IUI success, Maternal age, Motile sperm count, Pregnancy rate

Introduction

Globally, infertility affects 80 million people and an estimated one in 10 couples [1, 2]. Late marriages, modern-day stress and a lower sperm count have led to a high number of infertility cases in Malaysia. An estimated 300,000 couples in the 20 to 40 years age group experienced some form of infertility creating a large demand for fertility services [3].

In Malaysia, intrauterine insemination (IUI) is available and affordable to most infertile couples. Nearly all public hospitals offer infertility treatment until the level of IUI with higher reproductive technology within reach of a small number with financial resources. IUI was considered the best first line treatment and the most cost effective procedure for cervical hostility and moderate male infertility. There is ample evidence that mild ovulation stimulation coupled with IUI significantly improved the probability of conception in couples with unexplained infertility and moderate male infertility [4, 5].

There had been published information on IUI and prognostic factors associated with successful outcome in the local context [6, 7] but findings from a large group analysis would provide a more concrete basis for counseling patients on expectations and treatment options.

Materials and Methods

A retrospective study was undertaken on 297 couples who underwent 445 IUI cycles from Jan 2005-Mar 2006

This article was accepted: 21 November 2006
Corresponding Author: Ong Fee Bee, Department of O&G, Medical Faculty, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur

at an academic referral hospital. Subjects presented with varying infertility duration of at least two years. No exclusion criteria were used in patient selection except azoospermia. As long as tubal patency was demonstrable, IUI was offered. Couples were grouped according to primary infertility diagnosis based on existing medical history and investigations. Those classified as tubal factor infertility were defined as having any abnormality or surgery to one or both fallopian tubes. Those defined as idiopathic had normal hormonal profile, semen parameters, pelvic anatomy and ovulatory cycles. Age of the subjects was computed from the national identity card number.

Ovarian stimulation (OS) was achieved in women with clomiphene citrate (CC), gonadotrophin (Gn) alone or in combination (CCGn). CC (50-200mg) was customarily given for five days starting on the second day (D2) of the menstrual cycle while Gn, (50-250iu; Gonal-f, Serono Inc. USA; Puregon, Organon USA) began on D1 and continued until day of ovulation induction. CCGn regime began with CC on D2-6 followed by Gn on D7 until ovulation induction. Ultrasound evaluation usually began on D6 and repeated serially every 2-3 days. Human chorionic gonadotrophin 10,000iu (hCG, Pregnyl, Organon USA,) was given when the leading follicle reached 18-20mm in diameter. Intrauterine insemination was performed 36-42 hours after hCG injection.

The male subject was instructed to abstain from ejaculation for 2-7 days prior to IUI. On the morning of IUI, the male subject is required to clean and dry both hands and penis prior to collection. Fresh semen was collected into a sterile 100 ml container, carried out in a special room within the hospital. Semen analysis was performed after liquefaction according to WHO criteria[8]. Motile sperm concentration (MSC) was derived from progressive motility multiplied by sperm concentration per ml. Three sperm preparation methods were used in the laboratory namely swim up, two gradient column and simple wash. Only poor motility and relatively debris free ejaculates were processed via simple wash. The media used in semen preparation were commercial standards [Ferticult, Fertipro Belgium; GIII series, Zander IVF Florida USA, PureSperm 100, Nidacon, Sweden].

The final sperm preparation was adjusted to 0.4-0.6 ml[9]. Insemination was performed transvaginally with a semi-flexible catheter [Select IUI, Select Medical Systems USA; Wallace Artificial Insemination Catheter, Smiths Medical Int. Ltd. UK]. The patient remained supine for at least 20 minutes after the procedure to avoid flowback.

Luteal phase support consisted of progesterone thrice daily, orally and vaginal pessary [Duphaston 10mg; Laboratories Besins Iscovesco, Paris; Utrogestan 100mg, Solvay Pharmaceuticals BV, Holland]. Pregnancy was defined by a positive urine pregnancy test on day 21 post IUI followed by positive ultrasound findings.

Analysis was performed on 445 cycles of IUI. Age was unavailable for 14 women (17 cases) and 33 men who were in the armed forces or migrants. Data was incomplete in nine follicular tracking and a semen analysis respectively. Those with missing values were included in analysis to avoid generating bias as none occurred in a pregnant cycle. Statistical analysis was carried out using SPSS version 10. The number of subjects in every analysis was indicated in each result table. ANOVA, t-test, paired t-test, χ^2, Pearson's correlation and repeated multivariate analysis were used where appropriate. Significance was set at $p<0.05$.

Results

The subjects had a mean paternal and maternal age of 35.5±5.8 (n=264, range 24-59) and 33.0±4.7 (n=280, range 21-46) years respectively (Table I). The main causes of infertility were idiopathic (50%), endometriosis (17%) and polycystic ovarian syndrome (PCOS)/anovulation (15%).

The male factor diagnosis of 10% was not reflected by semen analysis carried out on the day of IUI as 31% of all cycles had poor semen parameters (Table II). Almost 10% of the subjects were oligoastenoteratozoospermic with another 23% oligozoospermic or astenozoospermic by WHO criteria.

On the whole, the average number of dominant follicles recruited was two with mean endometrial thickness (ET) of 10.0mm (Table III). Different OS regime showed dissimilar follicular development and ET. CC, Gn and CCGn were used in 47.4%, 45.8% and 6.3% of OS cycles respectively (Table IV). Two cycles of IUI were carried out without OS. CC cycles showed significantly poorer follicular recruitment and thinner ET (both $p<0.0005$) compared to Gn and CCGn regimes. OS by Gn recruited the most follicles and had the thickest ET with the consequence of IUI being performed the earliest at 13.9±2.0 days (p=0.001).

A total of 42 pregnancies resulted from 445 cycles for a clinical pregnancy rate (PR) of 9.4% per cycle (42/445) and 14.1% per couple (42/297). The majority (66.6%) underwent one cycle with 21.7% and 11.6% undergoing two or more cycles. PR per attempt did not decline with the number of IUI cycles performed although no pregnancies occurred beyond the 4th cycle. Almost all (97.6%) pregnancies were achieved within three cycles with a cumulative PR of 36.7% per four cycles (Table V).

PR per attempt depreciated significantly with age namely women aged 36 years and above having a lower PR, 11.8% vs. 4.4% (p=0.028). The presence of three follicles or one large follicle at time of IUI produced a PR of ~10%. No pregnancy was seen in subjects with ET<6mm measured on day of hCG injection, 11.7±2.3 day of the OS cycle. The highest PR was observed in CCGn cycles, 17.9% followed by Gn cycles 11.8% and 6.2% in CC cycles. PR per regime was not statistically different (p=0.091) being not unduly influenced by pre and post processed MSC or maternal age.

In cases of severe oligozoospermia a demonstrably lower PR of 1.4% (p=0.008) was seen. The lowest semen denominator that achieved pregnancy was progressive MSC of 4.9x106/ml fresh semen which yielded a post process MSC of 5.1x106/ml. This study showed IUI+OS to be beneficial for oligozoospermic couples as PR comparable to normozoospermic patients was achieved. A two fold higher PR (p<0.001) was seen when sperm motility was ≥30% compared to those with lesser progressive motility, 10.6% (37 pregnancies/349 cycles) vs. 5.3% (5/95).

Sperm preparation techniques significantly increased sperm motility (p<0.0005) but had no influence on PR. Swim up significantly improved progressive motility post processed whereas gradient column increased progressive motility, sperm concentration and MSC (Table VI).

The highest PR was achieved in subjects with infertility factor of PCOS/anovulation, endometriosis and idiopathic (Table VII). No pregnancies occurred in those with tubal abnormalities although one or both tubes were demonstrated to be patent prior to IUI. The difference in PR between causes of infertility was not statistically significant. Others encompassed cases with miscellaneous etiology of cancer, chronic illness and endocrine problems. The sole pregnancy in that group arose from a subject who formerly suffered from thyrotoxicosis.

IUI with OS was demonstrated to be a safe procedure with few complications. No complaints have arisen from the IUI procedure itself. Only two cases of ovarian hyperstimulation syndrome (OHSS) 0.04% occurred that required in patient care.

Further analysis showed that maternal age was negatively correlated to the number of follicles recruited (r=-0.30, p<0.0005) whereas paternal age was inversely related to sperm motility (r=-0.125, p=0.013). The age of husband and wife was closely correlated (r=0.73, p<0.0005) as expected. When maternal and paternal age, total and mature follicles, ET, number of cycles, MSC, method of sperm preparation and OS regime were analysed by repeated multivariate analysis, the predictor of pregnancy in the final model was maternal age (adjusted R^2 =0.013, standardized ß=0.122, p=0.011).

Table I: Characteristics of IUI subjects

Ethnicity	N (%)
(female, n=297)	
Malay	234 (78.8)
Chinese	39 (13.1)
Indian	15 (5.1)
Others	9 (3.0)
Primary sub-fertility	220 (74.1)
Primary infertility factors	
Idiopathic	149 (50.2)
Endometriosis	52 (17.5)
PCOS/Anovulation	45 (15.2)
Male factor	29 (9.8)
Tubal	14 (4.7)
Pelvic inflammatory disease	2 (0.7)
Fibroids (≥3, >2.5cm ∅)	3 (1.0)
Others	3 (1.0)

Table II: Male factor distribution on day of IUI

Male factor classification	N (%)
(n=296 couples)	
Normal	197 (66.6)
Oligozoospermia (<20 Million sperms per ml)	35 (11.8)
Astenozoospermia (<30% progressive motility)	35 (11.8)
Oligo-asteno-teratozoospermia (morphology <15%)	29 (9.8)
Raw semen parameters	**Mean±sd**
(n=444 cycles)	
Concentration ($x10^6$/ml); range 0.7-390.0	67.37±59.32
Progressive motility (%); range 4.2-84.0	43.05±16.58
Morphology (%); range 14.0-46.0	18.82± 5.16
Volume (ml); 0.5-6.5	2.77± 1.22
MSC per ml raw semen	**N (%)**
(n=444 cycles)	
<5 $x10^6$ (severe oligozoospermia)	71 (16.0)
5 to <10 $x10^6$ (oligozoospermia)	66 (14.9)
10 to <20 $x10^6$ (borderline oligozoospermia)	87 (19.6)
≥20 $x10^6$ (normal)	220 (49.5)

Table III: Overall IUI cycle parameters

Overall IUI cycle parameters	Mean±sd
(n=445)	
Total follicles	11.66±7.04
Large follicles (≥18mm diameter)	1.94±2.10
Endometrial thickness (mm)	10.06±2.58

Table IV: IUI Cycle parameters per ovarian stimulation regime

IUI cycle parameters per regime	CC (n=211)	Gn (n=204) Mean±sd	CCGn (n=28)
Total follicles*	8.34±4.28	14.02±7.85	15.11±6.94
Large follicles*	1.53±1.05	2.37±2.69	1.41±1.47
Endometrial thickness (mm)*	8.91±2.24	10.98±2.49	9.43±2.97
Day of IUI$	14.49±1.94	13.87±2.02	15.32±2.17

*p<0.0005; $p=0.001

Table V: Clinical pregnancy rate by maternal age, number of follicles, endometrial thickness, number of cycles, motile sperm count, method of sperm preparation and ovarian stimulation regime

Variables	Category				
Mat. age (n=428)	<25 yrs	26-30 yrs	31-35 yrs	36-40 yrs	41+ yrs
PR, n (%) #	2/11 (18.2)	17/128 (13.3)	18/175 (10.3)	2/78 (2.6)	3/36 (8.3)
IUI cycle (n=445)	1	2	3	4	5+
PR, n (%)	31/296 (10.5)	6/97 (6.2)	4/34 (11.8)	1/12 (8.3)	0/6 (0)
Fol.>18mm (n=442)	1	2	3	4	5+
PR, n (%)	25/248 (10.1)	4/86 (4.6)	3/39 (7.7)	2/31 (6.4)	7/38 (18.4)
Total fol. (n=442)	≤3	4-6	7-9	10-12	≥12
PR, n (%)	4/38 (10.5)	4/77 (5.2)	4/75 (5.3)	9/79 (11.3)	20/173 (11.6)
ET (n=437)	<6.0mm	6.0-8.9mm	9.0-11.9mm	12.0-14.9mm	15.0+mm
PR, n (%)	0/14 (0)	15/155 (9.7)	15/169 (8.9)	8/82 (9.8)	3/17 (17.6)
OS regime (n=445)	CC	CCGn	Gn	Natural	
PR, n (%)	13/211 (6.2)	5/28 (17.9)	24/204 (11.8)	0/2 (0)	
MSC (n=444)	<5x10^6/ml	5-<10x10^6/ml	10-<20x10^6/ml	≥20x10^6/ml	
PR, n (%)*	1/71 (1.4)	10/66 (15.2)	4/87 (4.6)	27/220 (12.3)	
Sp. Prep. (n=444)	Gradient	Swim up	Simple wash		
PR, n (%)	41/416 (9.9)	1/21 (4.8)	0/7 (0)		

*p=0.008; #p=0.028

Key: Pregnancy rate(PR); endometrial thickness(ET); follicles(fol); motile sperm count(MSC); sperm preparation method(Sp. Prep); ovarian stimulation(OS); clomiphene(CC); gonadotrophins(Gn).

Table VI: Sperm preparation techniques

Preparation method (n=444 cycles)	Motility[$](%)	Concentration (10^6/ml) Mean±sd	MSC (10^6/ml)
Pre-processed			
Gradient (N=416)	42.57±16.46	67.34± 59.42	32.64± 36.72
Swim up (N=21)	52.02±12.36*	84.48± 59.95	48.68± 37.09
Simple wash (N=7)	47.23±26.02	29.43± 56.71	14.92± 30.47
Post-processed			
Gradient[a]	86.93±13.36	89.31±161.22	81.11±156.81
Swim up[b]	88.65± 9.74	67.46± 47.37	63.57± 43.61
Simple wash	72.29±20.79#	19.34± 25.94	15.75± 21.07

[$]p<0.0005, pre vs. post process; *p=0.035; #p=0.014

[a]p<0.0005, motility; p=0.003, concentration; p<0.0005, MSC

[b]p<0.0005, motility

Table VII: Pregnancy rate versus causes of infertility

Causes of infertility (n=445)	N (%)
Idiopathic	23/209(11.0)
PCOS/Anovulation	10/76(13.2)
Endometriosis	7/59(11.9)
Male factor	1/71 (1.4)
Tubal	0/20 (0)
Fibroid	0/3 (0)
PID	0/2 (0)
Others	1/5(20.0)

Discussion

The findings in this study mirrored other reports whereby a younger maternal age, adequate motile sperm count and two or three mature follicles were good prognostic factors for successful IUI outcome. The clinical PR, 9.4% was comparable to the global average of 10% [10, 11, 12]. Sikandar et al indicated that in Pakistani women a younger maternal age, MSC >10 millions/ml and two or more mature follicles >16 mm were good prognostic factors for pregnancy [13]. Khalil *et al* reported a PR of 11.9% from over 2400 IUI cycles in Denmark if at the time of insemination, 3 to 4 mature follicles have developed and that at least five million motile sperms were available for insemination [14]. In concurrence, Dickey *et al* showed that PR was influenced by maternal age ≥43 years, poor semen quality, single pre-ovulatory follicle and infertility diagnoses. PR was shown to remain constant through four cycles and then fell significantly for diagnoses other than ovulatory dysfunction [15].

Accordingly, in our centre the highest PR was observed in women with the most follicles and ET≥15.0mm at the time of insemination. Maternal age was negatively correlated to the number of follicles recruited indicating diminished ovarian reserve as women aged. Subjects who became pregnant being younger had better ovarian response, with success increasing in tandem with the number of mature follicles present [16]. Similar to Sikandar *et al* [13] who specified an ET of >7mm, an acceptable PR was achieved when ET of ≥6mm was measured on day of hCG injection. Previous studies have indicated that ET did not serve as a good predictor of success especially in CC stimulated cycles [17]. ET was an outcome of follicular recruitment and thus, women who had adequate follicular development tended to have better ET as well.

Although the effect of age on PR is well established [18, 19], older subjects in our centre had a comparatively lower PR of 4.4% whereas European 2002 registry data achieved a clinical PR of 11.6% and 7.8% in women <40 and ≥40 years of age respectively 10. Partially accountable for the poorer outcome was the use of CC for OS in older women, unavoidable due to economic considerations. OS with CC followed by IUI was found to produce significantly lower PR in women aged 35 and older[20]. CC, an anti-estrogenic agent had a known effect of impairing endometrial development and cervical mucus in the face of good follicular development, resulting in a lower PR [21, 22].

A sequential treatment protocol was practiced in our centre whereby CC was the first line therapy offered to patients followed by combined CCGn if the subject showed adequate follicular development but poor ET when on CC. Gn were given to older women or those with poor follicular development on CC. Logic follows that milder infertility cases would have been resolved earlier leaving intractable cases with consequently poorer outcome for Gn cycles [15, 23].

The major causes of infertility namely idiopathic, endometriosis and ovarian were similar to an earlier study [7] although presently idiopathic infertility made up the largest group. The PR per cycle was comparable to Sahakyan et al who reported 13%, 12% and 10% overall fecundity for anovulatory, endometriosis and idiopathic infertility respectively [24]. In contrast to our findings whereby couples with tubal pathology[7] and severe male factor achieved low or no pregnancy, Sahakyan et al had a PR of 9% and 7%. On the other hand, Steures et al had implicated tubal pathology as an unfavourable predictor of IUI success from analysis of nearly 3400 Dutch couples who underwent 15000 cycles [25].

PR was shown to be generally low in male factor infertility regardless of OS regime [21, 26, 27, 28]. Studies have shown a significantly higher proportion of aneuploidy in severe male factor, inversely correlated to sperm concentration and progressive motility. The final outcome would likely be an increased in failed implantation and/or repeated abortion [29]. The low PR seen in the severe oligozoospermic group was also due to the added predicament of the female partner who presented with infertility factor of PCOS (n=10), endometriosis (n=13) and one each of fibroids and tubal pathology.

A lower PR observed in the subset of borderline oligozoospermia (10 to $<20 \times 10^6$ MSC/ml) could be a reflection of more severe problems in the female. Recently, a diminished ovarian reserve was shown in young (<30 years) normally cycling women. Ovarian response in women with idiopathic and mild male factor infertility undergoing in-vitro fertilization (IVF) have revealed a U shape relationship in older and younger women; a result of diminished quantitative response i.e. fewer follicles. It was suggested if standard infertility workup did not reveal any abnormality in young women, their ovarian reserve should be investigated [30].

In our centre, a semen threshold of $>5 \times 10^6$/ml MSC resulted in an acceptable PR. A lower insemination threshold of 1x106/ml MSC was reported by Berg *et al*[26]. In over 3000 IUI cycles, a plateau in PR of 7-10% per cycle was achieved following insemination of >$1x10^6$/ml MSC with a small increase seen at higher sperm concentration. Insemination of <1x106/ml motile sperm resulted in PR of <1% per cycle. The disparity could be due to the nature of our infertile population with over 80% male subjects being teratozoospermic[6, 31]. In the event normal morphology was <30% after sperm preparation, a minimum insemination number of $5x10^6$/ml motile sperms was advised, the rational being quantity compensated at least in part for the defective quality[32, 33]. Additionally, a two fold higher PR was observed when fresh semen motility was ≥30%[34], a variable that related inversely to paternal age.

A universal threshold whereby IUI can be performed with a satisfactory PR has not been determined although success was impaired with insemination of <$1x10^6$ MSC and <5% normal spermatozoa[35]. When <$1x10^6$/ml MSC were available after preparation, intracytoplasmic sperm injection (ICSI) may be the treatment of choice[36]. Below the minimal semen criteria, IVF or ICSI should be considered as it provided a better chance of pregnancy especially in couples with long standing infertility whereby the female was normal.

We chose to report PR versus fresh semen parameters rather than post processed sperm count in order to provide a cost effective clinical predictor. The use of post washed MSC would entail added time and expense to the patient as post washed MSC had to be established during the fertility workup rather than at insemination[37].

To summarise, factors related to the success of IUI included a younger maternal age, MSC>$5x10^6$/ml, adequate follicular and endometrial development. Those who became pregnant following IUI+OS were significantly younger and had better ovarian response with more follicles. PR per attempt reduced significantly in women aged 36 years and above. PR did not decline with subsequent IUI cycles although no pregnancy occurred after 4th attempt. A higher PR was seen in subjects with infertility causes of PCOS/anovulation, endometriosis and unexplained cases. Maternal age was negatively correlated to the number of follicles recruited whereas paternal age was inversely related to sperm motility. Repeated multivariate analysis showed the predictor of IUI success to be maternal age.

Results indicated IUI to be beneficial for oligozoospermic couples as PR comparable to normozoospermic patients was achieved. If reduced MSC was the primary infertility diagnosis with the wife likely to present with mild problems, IUI should be the treatment of choice[38]. Patients with poor prospects of severe male factor or tubal pathology should be encouraged to attempt IVF/ICSI earlier. Women ≥36 years old should be treated more aggressively i.e. with gonadotrophins and progress rapidly to IVF/ICSI following unsuccessful IUI as maternal age was crucial to success, an approach advocated by other IUI practitioners as well[14, 24].

The study being a retrospective analysis suffered from differences in participant characteristics and variable clinical approaches which resisted straightforward comparison. Subjects varied in regard to infertility factors, OS regime and semen preparation as well as difficult to discern factors such as insemination catheters[39] and ejaculatory abstinence interval prior to IUI[40], all of which have a bearing on the outcome. Nonetheless, due to the larger number of cycles analyzed, we were able to demonstrate the predictor associated with IUI success.

In conclusion, factors associated with IUI success included a younger maternal age, MSC>$5x10^6$/ml, adequate follicular and endometrial development. Modeling by multivariate analysis showed the predictor associated with successful outcome was maternal age.

Acknowledgements

We wish to thank Mrs Rita Zahra for her assistance in the MAC Unit. We also wish to acknowledge the contribution of the Ultrasound Unit and all its personnel towards our success.

References

1. Giudice LC. Infertility and the environment: the medical context. Semin Reprod Med. 2006; 24: 129-33.
2. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982-2002. Fertil Steril. 2006; 86: 516-23.
3. Samy FA. Sharp rise in infertility. The Star Online 2006; Feb 28; http://thestar.com.my/news/story.asp?file=/2006/2/28/nation/13521949&sec=nation
4. Balasch J. Gonadotrophin ovarian stimulation and intrauterine insemination for unexplained infertility. Reprod Biomed Online 2004; 9: 664-72.
5. Cohlen BJ. Should we continue performing intrauterine inseminations in the year 2004? Gynecol Obstet Invest 2005; 59: 3-13.
6. Omar MH, Ong FB, Adeeb NN, *et al.* Assessing the status of intrauterine insemination before forming a medically assisted conception unit. Med J Malaysia 1999; 54: 65-71.
7. Outcome of intrauterine insemination in patients with single patent tube: a 3 year review. Shamsir A, Murizah Z, MH Omar *et al.* Malaysian J Obstet Gynecol 2006; 8: 48-57.
8. World Health Organization. WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th Edition. Cambridge University Press, Cambridge 1999.
9. Franco JG, Baruffi RLR, Mauri AL, *et al.* Radiologic evaluation of incremental intrauterine instillation of contrast material. Fertil Steril 1992; 58: 1065-67.
10. Andersen AN, Gianaroli L, Felberbaum R, *et al.* [The European IVF-monitoring programme (EIM) for the European Society of Human Reproduction and Embryology (ESHRE)]. Assisted reproductive technology in Europe, 2002. Results generated from European registers by ESHRE. Hum Reprod. 2006; 21: 1680-97.
11. 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.
12. Zeyneloglu HB, Arici A, Olive DL, Duleba AJ. Comparison of intrauterine insemination with timed intercourse in superovulated cycles with gonadotrophins: a meta-analysis. Fertil Steril 1998; 69: 486-91.
13. Sikandar R, Virk S, Lakhani S, Rizvi J. Intrauterine insemination with controlled ovarian hyperstimulation in the treatment of subfertility. J Coll Physicians Surg Pak. 2005; 15: 782-85.
14. Khalil MR, Rasmussen PE, Erb K, *et al.* Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles. Acta Obstet Gynecol Scand 2001; 80: 74-81.
15. Dickey RP, Taylor SN, Lu PY, *et al.* Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. Fertil Steril 2002; 78: 1088-95.
16. Plosker SM, Jacobson W, Amato P. Predicting and optimizing success in an intrauterine insemination program. Hum Reprod 1994; 9: 1014-21.
17. Kolibianakis EM, Zikopoulos KA, Fatemi HM *et al.* Endometrial thickness cannot predict ongoing pregnancy achievement in cycles stimulated with clomiphene citrate for intrauterine insemination. Reprod Biomed Online 2004; 8: 115-18.
18. Brzechffa PR, Buyalos RP. Female and male partner age and menothrophin requirements influence pregnancy rates with human menopausal gonadotrophin therapy combined with intrauterine insemination. Hum Reprod 1997; 12: 29-33.
19. Corsan G, Trias A, Trout S, Kemman E. Ovulation combined intrauterine insemination in women aged 40 years of age and older: is it worthwhile? Hum Reprod 1996; 11: 1109-112.
20. Agarwal SK, Buyalos RP. Clomiphene citrate with intrauterine insemination: is it effective therapy in women above the age of 35 years? Fertil Steril 1996; 65: 759-63.
21. Arici A, Byrd W, Bradshaw K, *et al.* Evaluation of clomiphene citrate and human menopausal gonadotrophin treatment: a prospective, randomized, crossover study during intrauterine cycles. Fertil Steril 1994; 61: 314-18.
22. Homburg R. Clomiphene citrate – end of an era? A mini-review. Hum Reprod 2005; 20: 2043-51.
23. Dickey RP, Taylor SN, Lu PY, *et al.* Clomiphene citrate intrauterine insemination (IUI) before gonadotrophin IUI affects the pregnancy rate and the rate of high-order multiple pregnancies. Fertil Steril 2004; 81: 545-50.

24. Sahakyan M, Harlow BL, Hornstein MD. Influence of age, diagnosis and cycle number on pregnancy rates with gonadotrophin-induced controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril 1999; 72: 500-4.

25. Steures P, van der Steeg JW, Mol BW *et al*; CECERM (Collaborative Effort in Clinical Evaluation in Reproductive Medicine). Prediction of ongoing pregnancy after intrauterine insemination. Fertil Steril 2004; 82: 45-51.

26. 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.

27. Balasch J, Ballesca JL, Pimentel C, Creus M, Fabregues F, Vanrell JA. Late low dose follicle stimulating hormone for ovarian stimulation in intra-uterine insemination cycles. Hum Reprod 1994; 9: 1863-66.

28. Millingos S, Comhaire FH, Liapi A, Aravantinos D. The value of semen characteristics and tests of sperm function in selecting couples for intrauterine insemination. Eur J Obstet Gynecol Reprod Biol 1996; 64: 115-18.

29. Gianaroli L, Magli MC, Cavalli G *et al.* Frequency of aneuploidy in sperm from patients with extremely severe male factor infertility. Hum Reprod 2005; 20: 2140-52.

30. Goverde AJ, McDonnell J, Schats R, *et al.* Ovarian response to standard gonadotrophin stimulation for IVF is decreased not only in older but also in younger women in couples with idiopathic and male subfertility. Hum Reprod 2005; 20: 1573-77.

31. Ong FB, Adeeb N, Nasri N. The distribution of male infertility and the occurrence of different types of sperm abnormalities among patients attending an assisted conception unit. Sing J Obstet Gynecol 1998; 29: 25-33.

32. Nallella KP, Sharma RK, Aziz N, Agarwal A. Significance of sperm characteristics in the evaluation of male infertility. Fertil Steril 2006; 85: 629-34.

33. Wainer R, Albert M, Dorion A *et al.* Influence of the number of motile spermatozoa inseminated and of their morphology on the success of intrauterine insemination. Hum Reprod 2004; 19: 2060-65.

34. Yalti S, Gurbuz B, Sezer H, Celik S. Effects of semen characteristics on IUI combined with mild ovarian stimulation. Arch Androl 2004; 50: 239-46.

35. Ombelet W, Deblaere K, Bosmans E *et al.* Semen quality and intrauterine insemination. Reprod Biomed Online. 2003; 7: 485-92.

36. Tournaye H. Sperm and assisted reproduction. Minerva Urol Nefrol 2005; 57: 91-97.

37. van Weert JM, Repping S, Van Voorhis BJ, van der Veen F, Bossuyt PM, Mol BW. 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: 612-20.

38. Nan PM, Cohlen BJ, te-Velde ER *et al.* Intrauterine insemination or timed intercourse after ovarian stimulation for male subfertility? A controlled study. Hum Reprod 1994; 9: 2022-26.

39. Abou-Setta AM, Mansour RT, Al-Inany HG *et al.* Intrauterine insemination catheters for assisted reproduction: a systematic review and meta-analysis. Hum Reprod. 2006; 21: 1961-67.

40. Jurema MW, Vieira AD, Bankowski B, *et al.* Effect of ejaculatory abstinence period on the pregnancy rate after intrauterine insemination. Fertil Steril. 2005; 84: 678-81.