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. 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%. 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 gonadotrophin (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...
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]). 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 (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 2–4 ml of total sperm count multiply by percentage of motile sperm (Grade A, B and C) attached to a 2-ml syringe. If menstruation was delayed, plasma HCG was measured.

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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%. 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.

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>Pregnancies/cycle</td>
<td>82/507 (16.1)</td>
</tr>
<tr>
<td>Pregnancies/couple</td>
<td>82/317 (25.9)</td>
</tr>
<tr>
<td>Live births</td>
<td>66/82 (80.4)</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>11/82 (13.4)</td>
</tr>
<tr>
<td>Ectopic pregnancies</td>
<td>5/82 (6.2)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>6/82 (7.3)</td>
</tr>
</tbody>
</table>

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

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

*P <0.05  † P <0.01

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

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

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.

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 10, 11. 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.
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 and were attributed to the need for cycle monitoring or frustration for not becoming pregnant. 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