Comparison of Ongoing Pregnancy Rates and Multiple Pregnancy Rates of Intrauterine Insemination with Ovarian Stimulation Using Clomiphene Citrate Versus Gonadotrophin Protocols

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Objective: To compare the ongoing pregnancy rates and the multiple pregnancy rates of intrauterine insemination with ovarian stimulation using clomiphene citrate versus gonadotrophin protocols.
Methods: Retrospective cohort study.
Results: There were no statistically significant differences in the ongoing pregnancy rate and multiple pregnancy rate of intrauterine insemination following ovarian stimulation by clomiphene citrate and gonadotrophins. In the gonadotrophin group, eight patients had multiple pregnancies (seven had twins and one had triplets) while no subject in the clomiphene citrate group had multiple pregnancy.
Conclusion: The ongoing pregnancy rate with intrauterine insemination using clomiphene citrate stimulation was comparable to that using gonadotrophin stimulation. Intrauterine insemination with clomiphene citrate stimulation may be associated with a lower chance of multiple pregnancies when compared with gonadotrophin stimulation. Clomiphene citrate is a cheaper alternative to gonadotrophins in intrauterine insemination treatment.
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Introduction

Intrauterine insemination (IUI) with ovarian stimulation is used as an initial treatment for patients with unexplained or mild male factor subfertility. Both clomiphene citrate (CC) and gonadotrophins can be given for ovarian stimulation. Gonadotrophins have been compared with CC in recent randomised trials in terms of pregnancy outcomes and adverse effects in patients with unexplained infertility and male subfertility[1-3]. Using CC for ovarian stimulation in IUI has several advantages over using gonadotrophins. Being an oral medication, CC is less expensive and better accepted by patients as daily injections are not required. Lewis et al[4] found that there was no significant difference in the pregnancy rates of IUI treatment with ovarian stimulation using CC when follicular tracking was performed using pelvic ultrasound or by luteinising hormone (LH) surge. Thus, another advantage of using CC is the need for less labour-intensive monitoring with serial ultrasound for follicular tracking. As the two methods had no significant difference in pregnancy rates[1-3] and CC was possibly associated with a lower multiple pregnancy rate[1,2], our unit has moved from using gonadotrophins to CC for ovarian stimulation in IUI treatment since April 2011.

This study aimed to compare the ongoing pregnancy rates and the multiple pregnancy rates of IUI following ovarian stimulation by CC versus gonadotrophins. We hope that this review on the outcomes of a commonly adopted protocol in Hong Kong will be of local relevance.

Methods

This retrospective study was conducted at the Centre of Assisted Reproduction and Embryology, The University of Hong Kong, Queen Mary Hospital, Hong Kong. Ethics approval was obtained from the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster. Women who had undergone the first cycle of IUI with ovarian stimulation from October 2008 to September 2012 were identified. Women undergoing

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natural cycle IUI due to coital problems, having anovulation, and undergoing donor insemination were excluded from the study. Before April 2011, gonadotrophins were the standard agents used for ovarian stimulation in women undergoing IUI in our centre. We changed to adopt CC as the standard agent for IUI since April 2011. However, some patients who had been counselled for using gonadotrophins prior to the protocol change, or who had encountered thin endometrium in previous CC treatment prior to attending our centre continued with the gonadotrophin protocol.

In the gonadotrophin group, ovarian stimulation was achieved using human menopausal gonadotrophin (hMG) or recombinant follicle-stimulating hormone (rFSH) at 100-150 IU/day from day 3 of the cycle. Follicular growth was monitored with serial ultrasound scans and human chorionic gonadotrophin (hCG) was given when a leading follicle reached 18 mm in diameter. IUI was performed 38 hours after hCG injection. In the CC group, CC was started at a dose of 50-100 mg from day 2 to day 6 of the cycle. Patients attended the clinic daily from 18 days before the next expected period for the determination of serum 17ß-oestradiol (E2) and LH concentrations until the LH surge. LH surge was defined as an LH level of >20 IU/L and more than double of the mean LH level over the past 3 days. IUI was performed on the day after the LH surge. All outcomes were obtained retrospectively from patients' chart review and the assisted reproduction database. The primary outcome was the ongoing pregnancy rate. Secondary outcomes included the cumulative ongoing pregnancy rate, rates of cycle cancellation, ovarian hyperstimulation syndrome, and multiple pregnancy.

The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Results of continuous variables were given as mean ± standard deviation if normally distributed, and as median (interquartile range) if not normally distributed. Statistical comparison was carried out by Student's *t* test and Mann-Whitney *U* test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, where appropriate. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Version 19.0, Chicago [IL], US). A two-tailed p value of <0.05 was considered statistically significant.

Results

During the 4-year study period, 200 women meeting the inclusion criteria were identified. Twelve women were excluded as they had natural cycle IUI for coital problems or donor insemination. Overall, 141 subjects underwent 312 IUI cycles with gonadotrophin stimulation and 47 underwent 92 IUI cycles with CC stimulation during the study period; only subjects starting their first IUI cycle during the specified study period were included in the analysis. Each subject from both groups underwent a mean of two cycles. The median age in the gonadotrophin and CC groups was 34.0 and 33.4 years, respectively. The demographics of the study subjects are listed in Table 1. Results in both groups are comparable. Four patients who used CC in the first IUI cycle required gonadotrophin in subsequent cycles as they had thin endometrium (<8 mm) with CC treatment. All of them did not have successful ongoing pregnancy even after switching to gonadotrophin in subsequent IUI cycles. There was no statistically significant difference in the ongoing pregnancy rates in the first IUI cycles between the two groups (9.9% in the gonadotrophin group vs. 14.9% in the CC group). In all, 98 women in the gonadotrophin group and 25 in the CC group conceived or completed up to three IUI cycles. The cumulative ongoing pregnancy rate was comparable in both groups (33.7% vs. 36.0%; p=0.818). The pregnancy outcomes are listed in Table 2.

In our unit, an IUI cycle is cancelled if more than three dominant follicles, each measuring >16 mm, are noted on ultrasound assessment. Cycle cancellation was not required for any patient in this study. There were also

Table 1. Demographics of the study population

Characteristic	Median (interquartile range) or No. (%)		p Value
	Gonadotrophin group (n=141)	Clomiphene citrate group (n=47)	
Female age (years)	34.0 (24-41)	33.4 (23-42)	0.151
Male age (years)	37.2 (29-58)	36.5 (29-52)	0.600
Cause of subfertility			0.129
Male factor	78 (55.3)	18 (38.3)	
Mild endometriosis	7 (5.0)	3 (6.4)	
Unexplained	56 (39.7)	26 (55.3)	

no significant differences in the incidence of multiple pregnancy and ovarian hyperstimulation syndrome between the two groups (Table 3). In the gonadotrophin group, eight subjects had multiple pregnancies (seven had twins and one had triplets); the subject with triplets had mild ovarian hyperstimulation syndrome and was managed in the out-patient setting. Although these complications were not observed in any of the subjects in the CC group, the difference in the incidence rates between the two groups did not reach statistical significance (p=0.168 for multiple pregnancy and p=1.000 for ovarian hyperstimulation syndrome).

Discussion

This retrospective study showed that the ongoing pregnancy rate with IUI using CC stimulation was comparable to that using gonadotrophin stimulation. There was a possibility of fewer complications when IUI was performed using CC rather than gonadotrophins. In a recent randomised controlled trial, Berker et al[2] reported a lower ongoing pregnancy rate in patients with unexplained and male subfertility who underwent IUI with ovarian stimulation using CC compared with that using rFSH (9.6% vs. 15.6%; p=0.31), though the difference did not reach statistical significance. Although there are published randomised controlled trials[1-3] comparing the pregnancy outcomes of IUI using CC stimulation versus gonadotrophin stimulation, the outcomes may still vary depending on the population and the exact protocols adopted. We think that a review of the outcome based on a commonly adopted protocol in Hong Kong will be of local relevance. In our study, we found that pregnancy outcomes were comparable in both the gonadotrophin and CC groups (9.9% vs. 14.9%, p=0.422); these figures are similar to that reported in the current literature[1-3]. The difference in the pregnancy rates could be related to the different mechanisms of ovulation in the two groups (hCG induced in gonadotrophin group at leading follicle size of >18 mm in diameter, but spontaneous ovulation in CC group in which the leading follicle size usually exceeds >20 mm in diameter). However, as serial ultrasound scans were not routinely done in all patients undergoing IUI with CC stimulation, we did not have such data to confirm our hypothesis. Thin endometrial lining with use of CC appeared to be a drawback which required switching to gonadotrophin in a small number of patients. However, the four patients who were switched

Table 2. Number of cycles, ovarian stimulation characteristics, and pregnancy outcomes in the gonadotrophin and clomiphene citrate groups

Item	No. (%) or mean ± standard deviation		p Value
	Gonadotrophin group	Clomiphene citrate group	
Total No. of cycles	312	92	-
First cycle	141	47	-
Second cycle	97	30	-
Third cycle or later	74	15	-
Dosage of gonadotrophin (IU)	1007.1 ± 631.4	Not applicable	-
No. of follicles >16 mm 2 days before intrauterine insemination	1.17 ± 0.60	Not available	-
Ongoing pregnancy rate of the first cycle	14/141 (9.9)	7/47 (14.9)	0.422
Cumulative ongoing pregnancy rate of three cycles	33/98 (33.7)	9/25 (36.0)	0.818
Early miscarriage	5/312 (1.6)	2/92 (2.2)	0.359
Ectopic pregnancy	2/312 (0.6)	0/92	1.000
Molar pregnancy	0/312	1/92 (1.1)	0.228

Table 3. Adverse outcomes in the gonadotrophin and clomiphene citrate groups

Item	No. (%)		p Value
	Gonadotrophin group	Clomiphene citrate group	
No. of cycles cancelled	0	0	-
Multiple pregnancy	8/33 (24.2)	0/9	0.168
Ovarian hyperstimulation syndrome	1/312 (0.3)	0/92	1.000

to gonadotrophin did not achieve successful pregnancies. According to Reindollar et al[5], there is no added value of IUI with gonadotrophin stimulation in patients failing IUI with CC stimulation. However, only four patients in our cohort fell into this category and the sample size was inadequate to draw any conclusion.

It was observed that more patients suffered from male factor subfertility in the gonadotrophin group than in the CC group. This was likely due to the new 2010 World Health Organization reference values for semen characteristics[6]. This probably led to the same group of patients previously labelled to have male factor subfertility to later become those with unexplained subfertility. However, their management did not differ and they were still being offered IUI as the first-line treatment. According to most recent publications[7,8], including the United Kingdom National Institute for Health and Clinical Excellence guidelines[9], IUI may not be a cost-effective treatment modality for male factor or unexplained subfertility. However, since many in-vitro fertilisation programmes may have considerable waiting time, IUI may be offered as an interim treatment. For this to be offered in the most cost-effective way, the use of CC instead of gonadotrophin should be considered because it is relatively cheaper, does not need monitoring, and is associated with lower risk of complications.

CC has the benefits of being an oral medication leading to better acceptance by patients, and requiring less labour-intensive sonographic monitoring for follicular tracking. In our study, the mean dosage of gonadotrophins used per cycle was around 1000 IU, making the treatment more expensive than CC (according to the authors' hospital, the cost of CC was HK$1.8 per 50 mg tablet versus HK$ 66.9 per 75 IU of hMG). Since CC is less likely than gonadotrophins to result in multifollicular development, there was lower risk of ovarian hyperstimulation syndrome as shown in our data (0% vs. 0.3% p=1.000), as well as that of multiple pregnancies (0% vs. 24.2%; p=0.168), though not statistically significant due to the limitation of the small sample size in the CC group in our cohort. Another limitation of our study was the retrospective design. However, our results did provide some evidence of local relevance for a move towards the use of CC instead of gonadotrophins for ovarian stimulation in IUI treatment for male factor or unexplained subfertility.

Conclusion

The ongoing pregnancy rate with IUI using CC stimulation was comparable to that using gonadotrophin stimulation. IUI with CC stimulation may be associated with a lower chance of multiple pregnancies than with gonadotrophin stimulation. CC is a cheaper alternative to gonadotrophins in IUI treatment.

Declaration

The authors declared no conflict of interest in this study.

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