

The efficacy of conversion from IUI to IVF-ET in infertility patients with hyper-response to ovulation induction: A retrospective study

Yiping Zhong^{a#}, Jin Li^{b#}, Ying Ying^a, Haitao Wu^a, Canquan Zhou^a, Yanwen Xu^a, Qiong Wang^a, Jie Li^a, Xiaoting Shen^a

Background. The aim of the study was to determine the efficacy of *in vitro* fertilization and embryo transfer (IVF-ET) in patients with hyper-response to ovulation induction for intrauterine insemination (IUI).

Methods. Patients with polycystic ovary syndrome (PCOS) who were initially treated with IUI in our centre between Jan 2007 and Oct 2010 were retrospectively analyzed. The ovarian hyper-stimulation syndrome (OHSS) found in 50 patients was then treated with IVF-ET following informed consent.

Results. The fresh transfer had 42 cycles and a total of 87 embryos were transferred. Urine pregnancy tests were positive in 15 patients and fetal heart beat was detected in 12 patients by transvaginal ultrasound, from which 3 patients had two fetuses, 2 patients had three fetuses, and 7 patients had a single fetus. The overall clinical pregnancy rate was 28.5% (12/42) for the fresh embryo transfer. A total of 21 cycles of frozen embryo transfer with up to 55 embryos were conducted for patients who were not pregnant at the end of fresh embryo transfer cycles or who did not receive fresh embryo transfer in the first place. Urine pregnancy tests were positive in 10 patients and fetal heart beat was detected in 8 patients. The clinical pregnancy rate was 38.1% (8/21) for frozen embryo transfer.

Conclusion. We conclude that IVF-ET is an effective method for patients with hyper-response to ovulation induction in IUI.

Key words: polycystic ovary syndrome, in vitro fertilization and embryo transfer, ovulation induction, intrauterine insemination

Received: September 9, 2011; Accepted with revision: April 12, 2012; Available online: June 1, 2012

<http://dx.doi.org/10.5507/bp.2012.044>

^aReproductive Medicine Center, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, 510080

^bGuangdong No.2 Provincial People's Hospital, Guangzhou, China, 510000

[#]Authors contributed equally to the work

Corresponding author: Canquan Zhou, e-mail: zhoucanquan@hotmail.com

INTRODUCTION

With the advance of assisted reproductive technology, a combination of ovulation induction with intrauterine insemination (IUI) has achieved great success in the treatment of infertility. However, the pregnancy rate remains still unstable and depends on the condition of each individual case. To select the appropriate time window for IUI, the common way is to utilize the natural cycle or ovulation induction and monitor the follicle phase. Cycle-stimulated or non-cycle-stimulated IUI is considered as the first-line treatment for infertility caused by common etiological factors, including asthenozoospermia, semen liquefaction, sexual dysfunction, abnormal secretion of the female cervical mucus, and immunological complications^{1,2}. In addition, many retrospective and prospective studies have confirmed that using gonadotropin (Gn) to stimulate ovary and increase the number of follicles can achieve a better fertilization and implantation rate, thus ultimately improving the pregnancy rate³.

Although this approach generally increases the clinical pregnancy rate, a subset of hyper-responsive patients reports multiple follicle development and over-stimulation of the ovary, resulting in an increased risk of multiple pregnancy, preterm birth, miscarriage, and obstetric complications.

For these patients, successful pregnancy depends on careful control of the cycles, adjustment of the Gn dose, cancellation of the cycle or use of *in vitro* fertilization and embryo transfer (IVF-ET). The level of estradiol (E2) and the number of follicles determine whether the cycles need to be cancelled or IVF-ET should be performed. Fortunately, with the development and application of gonadotropin-releasing hormone analogues (GnRH-a), the conversion from IUI to IVF-ET becomes more feasible. Furthermore, cycle cancellation is frustrating for both the patients and physicians, and poses huge burdens, both psychologically and financially, on the patients and their families. The conversion from IUI to IVF-ET can largely avoid this problem.

Interestingly, to date, few studies have investigated the efficacy of the conversion from IUI to IVF-ET. In this present study, we directly addressed this and reported the efficacy of IVF-ET in patients who suffered from hyper-response to ovulation induction for IUI.

MATERIALS AND METHODS

Subjects

All the subjects in this study were chosen from patients admitted to the Center for Reproductive Medicine

at the First Affiliated Hospital of Sun Yat-sen University between Jan 2007 and Oct 2010. The study was approved by the ethics committee of Sun Yat-sen University and written consent was obtained from all subjects. Patients with liver and kidney disorders, acute or chronic infectious diseases and reproductive tract inflammation were excluded. All subjects had polycystic ovary syndrome (PCOS). Oviduct liquid passing test, hysterosalpingography and/or laparoscopy examinations confirmed that at least one side of the oviduct was clear. All patients received IUI with informed consent. Among these patients, 50 cases displayed hyper-response of the ovary to the ovulation induction drugs and were switched to IVF-ET treatment with further informed consent. Infertility was caused by ovulation failure, cervical factors, immunological factors, mild endometriosis, male factors (such as asthenozoospermia and semen liquefaction), and other unexplained infertility.

Conversion from IUI to IVF-ET

A total of 50 patients had 50 cycles. Starting 3-5 days after the menstrual cycle, the basic evaluation was conducted by ultrasound examination. If the size of the poly-cysts was smaller than 10 mm, medication was initiated with commonly prescribed Gn, such as human menopausal gonadotropin (HMG) or follicle-stimulating hormone (FSH), at the dose of 75-150 IU. After constant medication for 4-6 days, transvaginal B-ultrasound examination was performed to monitor the development of follicles and the dose of the drugs was adjusted accordingly. Based on our clinical experience and previous literature, hyper-response to Gn was operationally defined as the occurrence of more than 4 follicles with a diameter larger than 14 mm or the level of E2 higher than 1500 pg/mL (ref.⁴). Once hyper-response was found, we consulted with the patients and decided whether the cycle needed to be cancelled or IVF-ET needed to be performed. Most of the patients consented to switch to IVF-ET. If more than 3 follicles had a diameter larger than 17 mm or more than 2 follicles had a diameter larger than 18 mm, or the urine luteinizing hormone (LH) test was positive, human chorionic gonadotropin (HCG) was injected intramuscularly at a dose of 5,000-10,000 IU. Approximately 35-36 h after the HCG injection, vaginal ultrasound-guided oocyte retrieval was performed by the puncture of ovary. Three days after the oocyte retrieval, embryo transfer was conducted. Luteal support was accomplished by intramuscular injection of progesterone at a dose of 40 mg per day, or intramuscular injection of 2000 IU HCG every three

days for a total of 4 days, or utilization of progesterone vaginally. Fourteen days after the embryo transfer, a morning urine pregnancy test was performed. If the pregnancy test turned out to be positive, the medication was continued. The occurrence of the embryo sac by ultrasound examination 3 weeks later indicated clinical pregnancy. If the embryo sac examination was negative, the medication was terminated.

Semen collection and processing

According to World Health Organization standard procedures, semen samples from the patients' couples were collected after 3-7 days of sex abstinence using the masturbation sperm retrieval method. Semen samples were delivered to the laboratory within 30 min. After gradient centrifugation and upstream processing, the sperm concentration was adjusted to 1×10^6 /mL. The volume of the semen for fertilization was 0.2-0.5 mL. Regular testing was performed on the semen samples before and after washing.

Statistical analysis

The data were expressed as mean \pm standard deviation (SD). The statistical analysis was performed using Microsoft Excel software.

RESULTS

Basic clinical information of the subjects

The average age of the subjects was 30.90 ± 4.02 yr, ranging from 23 to 42 yr. Of the patients, 33 had primary infertility and 17 had secondary infertility. The average duration of infertility was 4.82 ± 3.16 yr, ranging from 1 to 15 yr. The average body mass index (BMI) was 20.46 ± 1.97 , ranging from 16.80 to 27.34. The average level of basic FSH was 4.82 ± 1.50 IU/L, ranging from 0.5 to 7.28 IU/L. The average level of LH was 6.31 ± 5.29 IU/L, ranging from 0.7 to 26.43 IU/L. The average level of prolactin (PRL) was 19.89 ± 9.66 ng/mL, ranging from 4.3 to 45.74 ng/mL. The average level of E2 was 40.40 ± 21.87 pg/mL, ranging from 10 to 98 pg/mL. The average level of testosterone (T) was 0.82 ± 0.50 ng/mL, ranging from 0.07 to 2.75 ng/mL (Table 1).

Cycle parameters of the patients

The total dose of Gn used was 1339.25 ± 826.74 IU, ranging from 450 to 2200 IU. The average number of follicles larger than 14 mm was 8.24 ± 2.98 , ranging from 4

Table 1. Basic clinical information of the subjects.

Conversion from IUI to IVF-ET	Age (yr)	duration of infertility (yr)	BMI (kg ² /cm)	Basic FSH (IU/L)	LH (IU/L)	PRL (ng/mL)	E2 (pg/mL)	T (ng/mL)
	30.90 \pm 4.02	4.82 \pm 3.16	20.46 \pm 1.97	4.82 \pm 1.50	6.31 \pm 5.29	19.89 \pm 9.66	40.40 \pm 21.87	0.82 \pm 0.50

to 22. Ovum was collected from 49 patients with an average number of 14.37 ± 7.76 , ranging from 2 to 35. Ovum was not collected from 1 patient. Ovum was fertilized in 49 patients. The average number of fertilized ovum was 7.65 ± 5.03 , ranging from 1 to 20. The average number of normal embryogenesis was 7.44 ± 4.92 , ranging from 1 to 20. The average number of available embryos was 5.29 ± 4.20 , ranging from 1 to 18. The average thickness of the endometrium was 10.85 ± 2.43 mm, ranging from 6 to 19mm when HCG was injected (Table 2).

Clinical efficacy of conversion from IUI to IVF-ET

Fresh embryo transfer was cancelled in 6 cases to prevent the occurrence of ovarian hyper-stimulation syndrome (OHSS). The fresh transfer had 42 cycles and a total of 87 embryos were transferred. Urine pregnancy test showed positive in 15 patients and fetal heart beat was detected in 12 patients by transvaginal ultrasound, of which 3 patients had two fetuses, 2 patients had three fetuses, and 7 patients had single fetus. In the remaining 3 cases, extrauterine pregnancy occurred in 1 patient and no fetal heart beat was detected in 2 patients. The overall clinical pregnancy rate of IVF-ET was 28.5% (12/42). Among the 6 patients who did not receive fresh embryo transfer, 1 patient to date has not undergone embryo transfer yet. In another case, after thawing, the frozen embryo was completed lyzed and thus no transfer was performed. A total of 21 cycles of frozen embryo transfer with up to 55 embryos were conducted for the patients who were not pregnant at the end of fresh embryo transfer cycles or who did not receive fresh embryo transfer in the first place. Urine pregnancy test was positive in 10 patients and fetal heart beat was detected in 8 patients by transvaginal ultrasound, of which 2 patients had two fetuses, 1 patient had three fetuses, and 5 patients had single fetus. For the remaining 2 cases, no fetal heart beat was detected in 1 patient and biochemical pregnancy occurred in 1 patient. The clinical pregnancy rate was 38.1% (8/21) (Table 3).

DISCUSSION

In our hospital, the cycle pregnancy rate of patients receiving IUI treatment fluctuates between 8% and 15%. The fresh cycle pregnancy rate is 28.5% and the frozen cycle pregnancy rate is 38.1%, which are slightly lower than those reported (57% and 48%, respectively) (ref.^{4,5}). A randomized, case-control study reveals that in infertility patients caused by male factors or mild endometriosis, the live birth rate of artificial insemination for patients with mild ovarian hyper-stimulation is higher than that for patients without any condition⁶. A recent comprehensive analysis of patients with unexplained infertility shows that the pregnancy rate of artificial insemination with monitored ovulation cycles is 4%. In comparison, the natural pregnancy rate guided by mild hyper-stimulation of cycles is 8%. Moreover, the pregnancy rate of artificial insemination combined with mild hyper-stimulation of cycles can reach 18% (ref.⁷).

In this study, all 50 patients who converted from IUI to IVF were hyper-responders. Based on the Rotterdam criteria, all patients were diagnosed as PCOS, which was considered an indication of potential hyper-responder. For these patients, the traditional effective treatment approach for infertility, the IUI combined with ovulation induction, has profound disadvantages including high rates of cycle cancellation and multiple fetal implantations⁸. Previous studies have showed that the rate of multiple fetal implantations is 7.5-29% (ref.⁹) in patients receiving IUI and ovarian stimulation¹⁰.

Most previous studies which compared the pregnancy rate between the IVF group and the conversion from IUI to IVF group reported that the clinical pregnancy rate was similar between the two groups. However, the implantation rate in the conversion from IUI to IVF group was much higher than that in the regular IVF group⁴. A related finding is that the E2 level in the conversion from IUI to IVF group was significantly lower than that in the

Table 2. Cycle parameters of the patients.

Conversion from IUI to IVF-ET	Gn total dose	Number of follicles \geq 14mm	Thickness of the endometrium (mm)	Ovum number	Number of fertilized ovum	Number of normal embryo-genesis	Number of available embryos
	1339.25 \pm 826.74	8.24 \pm 2.98	10.85 \pm 2.43	14.37 \pm 7.76	7.65 \pm 5.03	7.44 \pm 4.92	5.29 \pm 4.20

Table 3. Clinical efficacy of conversion from IUI to IVF-ET.

Group	Cycles	Embryos transferred	Clinical pregnancy rate	Biochemical pregnancy	Spontaneous abortion	Oviductal pregnancy	Single fetus	Two fetuses	Three fetuses
Fresh transfer	42	87	(12/42) 28.5%	0	2	1	7	3	2
Frozen transfer	21	55	(8/21) 38.1%	1	1	0	5	2	1

regular IVF group. High levels of E2 may increase uterine contraction and thus adversely affect the IVF implantation rate. However, some other studies report opposite findings¹¹.

The application of Gn for ovulation cycle stimulation and IUI treatment has the following characteristics. Firstly, Gn improves the quality of the eggs and sperms during the therapeutic cycle, which increases the probability of pregnancy¹². Secondly, administration of HMG can correct a variety of abnormalities caused by critical luteal dysfunction, including low LH peak, abnormal LH secretion, abnormal follicular development, low levels of E2 secretion cycle, luteinized unruptured follicle syndrome, and ovarian incompetence. Thirdly, recombinant Gn can ameliorate the low levels of FSH in patients with PCOS. Fourthly, direct injection of treated sperms into the uterine cavity provides a reasonable therapy for the treatment of infertility caused by oligospermia, asthenospermia and cervical factors. Finally, application of Gn can achieve a remarkable pregnancy rate of 23% for patients with unexplained infertility. To sum up, it is a simple, effective, and economic method¹³.

If such complications happen in IUI medical centers with IVF capabilities, the patients should be offered IVF treatment as an alternative. For IUI medical centers without IVF facilities, the patients should be transferred to other hospitals where IVF is routinely performed.

Conversion to IVF can reduce the occurrence of complications and potential risks that the patients may experience. More importantly, larger numbers of ova and embryos can be obtained after conversion to IVF and this increases the pregnancy rate. Compared to controlled ovarian hyperstimulation (COH) followed by IVF, the conversion from IUI to IVF uses lower doses of Gn. For this reason, patients can have better endometrial receptivity, the implantation rate can be increased, and the cost can be lowered¹⁴. When there are more than 4 follicles larger than 14 mm on the day HCG was injected; multiple follicles can develop¹⁵. In the present study, the average number of follicles obtained from 49 patients was 14.37, which is consistent with previous findings. These results suggest that IVF treatment should be considered when there are more than 4 dominant follicles larger than 14 mm on the day HCG is injected.

The selection of appropriate ovulation stimulation program and handling of multiple follicle development should be considered with extreme caution for the treatment of infertility patients with hyper-responses. PCOS patients have the potential for hyper response to ovulation stimulation. Therefore, cancellation of the cycle or conversion to IVF should be well-prepared ahead of ovulation stimulation. For example, electrocardiogram, chest X-ray and other IVF-related examinations should be performed in advance. However, there is relatively insufficient support to conduct the tube baby test (body check). Cycle cancellation can prevent the occurrence of OHSS, but it also poses huge burdens on the patients, both psychologically and financially. In medical centers with the ability to perform IVF, most patients with hyper-response to

ovulation stimulation prefer conversion to IVF to cycle cancellation.

One study has reported that a combination of follicle rupture and IUI can be used in patients with multiple follicle development during the process of ovulation stimulation¹⁶. On the one hand, this can increase the possibility for pregnancy. On the other hand, rupture of the follicles and controlling the number of the implanted embryos can reduce the likelihood of multiple pregnancy and overstimulation of the ovary. Multiple pregnancy rates can also be reduced by aspiration of supplementary follicles followed by IUI (ref.¹⁵). In the present study, we also managed to aspirate some of the ova using ultrasound-guided follicle aspiration. The aspirated ovum was used for IVF and the formed embryo was frozen. The remaining 1 or 2 mature follicles were used for IUI treatment or directed natural pregnancy. This strategy worked well for the most of our patients.

Application of an antagonist is also feasible during the process of ovarian stimulation and IUI treatment. However, this reduces the clinical pregnancy rate, possibly due to its impact on the endometrial receptivity. Rather than pure antagonist treatment, mild stimulation of the ovary can be achieved by personalized therapeutic program. For example, during the first ovulation stimulation, clomiphene or letrozole may be individually administered; whereas in the later stage, Gn can be used for ovulation stimulation. Finally, for those patients with high BMI, appropriate pretreatment should be conducted before *in vitro* reproductive techniques are used. For example, improvements of living habits and increasing the physical activity can be beneficial for losing weight.

In summary, our results demonstrate that conversion to IVF-ET is an efficient method for patients with hyper-responses to ovulation induction during regular IUI stimulation cycle. In addition, it has a relatively high pregnancy rate. However, the choice of *in vitro* reproductive technique varies in each case. For example, single embryo transfer may be considered to avoid multiple pregnancies for those patients with relatively good conditions⁵. The limitation of this study is small number of subjects and lack of a control group in which the hyper-responsive patients remain on IUI treatment. We believe that prospective, multi-site, randomized, and case-control studies are urgently need to determine the feasibility and effectiveness of conversion to IVF in hyper-responsive patients with unknown causes or male factors infertility.

ACKNOWLEDGEMENT

The work was supported by science and technology projects of Guangdong Province (2009B030801155) and research projects for the members of the Guangdong population and family planning committee (2010243).

CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Karande VC, Korn A, Morris R, Rao R, Balin M, Rinehart J, Dohn K, Gleicher N. Prospective randomized trial comparing the outcome and cost of in vitro fertilization with that of a traditional treatment algorithm as first-line therapy for couples with infertility. *Fertil Steril* 1999;71:468-75.
2. Pashayan N, Lyratzopoulos G, Mathur R. Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. *BMC Health Serv Res* 2006;6:80.
3. Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, Steinkampf MP. Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998;70:207-13.
4. Nisker J, Tummon I, Daniel S, Kaplan B, Yuzpe A. Conversion of cycles involving ovarian hyperstimulation with intrauterine insemination to in-vitro fertilisation. *Human Reproduction* 1994;9(3):406-8.
5. Antman AM, Politch JA, Ginsburg ES. Conversion of high-response gonadotropin intrauterine insemination cycles to in-vitro fertilization results in excellent ongoing pregnancy rates. *Fertil Steril* 2002;77:715-22.
6. Tummon IS, Asher JL, Martin JSB, Tulandi T. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertil Steril* 1997;68:8-7.
7. Haydardedeoglu B, Bagis T, Simsek E, Cok T, Hacivelioglu SO, Erkanli S. The impact of rescue in vitro fertilization converted from high-response gonadotropin intrauterine insemination cycles in terms of implantation and pregnancy rates as compared with matched controls. *Fertil Steril* 2009;92:137-42.
8. Olufowobi O, Sharif K, Papaioannou S, Mohamed H, Neelakantan D, Afnan M. Role of rescue IVF-ET treatment in the management of high response in stimulated IUI cycles. *J Obstet Gynaecol* 2005;25:166-8.
9. Schenker JG, Yarkoni S, Granat M. Multiple pregnancies following induction of ovulation. *Fertil Steril* 1981;35:105-23.
10. Callahan TL, Hall JE, Ettner SL, Christiansen CL, Greene MF, Crowley WF Jr. The economic impact of multiple-gestation pregnancies and the contribution of assisted-reproduction techniques to their incidence. *N Engl J Med* 1994;331:244-9.
11. Valbuena D, Simón C, Romero JL, Remohí J, Pellicer A. Factors responsible for multiple pregnancies after ovarian stimulation and intrauterine insemination with gonadotropins. *J Assist Reprod Genet* 1996;13:663-8.
12. Zarrilli S, Paesano L, Colao A, Mirone V, Lombardi G, De Rosa M. FSH treatment improves sperm function in patients after varicocelectomy. *J Endocrinol Invest*. 2000;23(2):68-73.
13. Guanglun Z. Modern assisted reproductive technology. Beijing: People's Medical Publishing House, 2005. p132-4.
14. Xianhong T. The natural cycle of IVF - ET in assisted reproductive technology in the application. *Foreign family planning/reproductive health branch* 2006;25(1):18-9.
15. De Geyter C, De Geyter M, Nieschlag E. Low multiple pregnancy rates and reduced frequency of cancellation after ovulation induction with gonadotropins, if eventual supernumerary follicles are aspirated to prevent polyovulation. *J Assist Reprod Genet* 1998;15:111-6.
16. Kun-ming L, Xiao-ming T, Hui-fen C, Fan Y, Zhi-qin C, Li-ping Z, Jianzhi Y, Yu W, Jia-ping P, Jing-yu S. Preliminary Discussion of Patients of Multi-follicle Development during Induced Ovulation Altered to IVF-ET or Mature Follicle Puncture +IUI. *Reproduc contracep* 2008;28(6):1-5.