Rescue in vitro fertilization using a GnRH antagonist in hyper-responders from gonadotropin intrauterine insemination (IUI) cycles

Jacques Balayla · Louis Granger · Pierre St-Michel ·
Marc Villeneuve · Jean-Yves Fontaine ·
Pascal Desrosiers · Elias M. Dahdouh

Received: 1 April 2013 / Accepted: 17 May 2013 / Published online: 30 May 2013
© Springer Science+Business Media New York 2013

Abstract

Objective To evaluate the outcomes in the conversion of high-response gonadotropin intrauterine insemination (IUI) cycles to “rescue” in vitro fertilization (IVF) using a Gonadotropin-Releasing Hormone (GnRH) antagonist, with regards to implantation rates, pregnancy rates, cost, and ovarian hyperstimulation syndrome (OHSS) as compared to matched, hyper-responder, IVF controls.

Methods This prospective cohort study was conducted between January 2007 and December 2009 at our institution. In order to decrease high-order multiple pregnancy, minimize the incidence of OHSS, and avoid cycle cancellation, high-response stimulated-IUI patients opted to convert to “rescue” IVF using the GnRH antagonist cetrorelix acetate. We then compared their clinical outcomes with matched patients from high-response IVF cycles of the standard long mid-luteal GnRH agonist protocol (14 or more collected oocytes). Only cases of conventional IVF without intra-cytoplasmic sperm injection (ICSI) were included in the control group.

Capsule Conversion of high-response gonadotropin-IUI cycles to “rescue” IVF using a GnRH antagonist is a cost-effective strategy that produces better results than regular IVF.

J. Balayla · L. Granger · E. M. Dahdouh
Department of Obstetrics and Gynecology, University of Montreal,
Montreal, Canada

L. Granger · P. St-Michel · M. Villeneuve · J.-Y. Fontaine ·
E. M. Dahdouh (✉)
PROCREA Clinics, 1361 Beaumont Avenue (Suite 301),
Montreal, Quebec, Canada H3P 2W3
e-mail: eliasdahdouh@yahoo.com

L. Granger · P. Desrosiers · E. M. Dahdouh
CHU Sainte-Justine, ART Centre, Montreal, Canada

Results Out of 184 patients undergoing stimulated-IUI cycles with gonadotropins, 87 patients developed a hyper-response, and 20 opted to convert to “rescue” IVF. These patients were compared with 157 matched, hyper responder IVF controls from our registry. The implantation rate was 25.6 % in the “rescue” IVF group and 20.7 % in the control IVF group ($p<0.0047$). The ongoing clinical pregnancy rate per embryo transfer was 45.0 % and 33.6 % in the “rescue” IVF and the control IVF groups, respectively ($p<0.0001$). The mean duration of stimulation was comparable between cohorts (10.0 vs.10.4 days, $p=0.6324$). The mean dose of gonadotropin used per cycle was higher in the control group, 2664 international units (IU) of follicle stimulation hormone (FSH) compared to 1450 IU of FSH in the “rescue” IVF group ($p<0.0001$). The incidence of severe OHSS is also higher in the control group, 5.1 % versus no cases in the “rescue” IVF group ($p<0.0001$).

Conclusion Our study demonstrates that conversion of high-response gonadotropin-IUI cycles to “rescue” IVF using a GnRH antagonist is a cost-effective strategy that produces better results than regular IVF with relatively minimal morbidity, and shorter duration to achieve pregnancy. Implantation and ongoing clinical pregnancy rates tend to be higher than those from hyper-responder regular IVF patients.

Keywords Stimulated IUI · Hyper-responders · Rescue IVF · GnRH antagonist

Abbreviations

IUI	Intrauterine insemination
OHSS	Ovarian hyperstimulation syndrome
GnRH	Gonadotropin releasing hormone
LH	Luteinizing hormone

FSH	Follicle stimulating hormone
IVF	In vitro fertilization
hCG	Human chorionic gonadotropin
ICSI	Intra-cytoplasmic sperm injection
DET	Double embryo transfer
PR	Pregnancy rate
CPR	Clinical pregnancy rate
CPR/ET	Ongoing clinical pregnancy rate per embryo transfer
PR/ET	Biochemical pregnancy rate per embryo transfer
IR	Implantation rate
hMG	Human menopausal gonadotropin
E2	17 β -estradiol
eSET	Elective single embryo transfer
ART	Assisted reproductive techniques

Introduction

Intrauterine insemination (IUI) has been the first-line treatment of male factor subfertility, unexplained infertility, as well as certain unilateral tubal disorders leading to sterility. Ovulation in IUI can come from a natural cycle, as in unstimulated IUI, or can be induced with the use of gonadotropin injections or anti-estrogenic agents. The latter is defined as a “stimulated IUI cycle”. In stimulated IUI cycles, it is theorized that controlled ovulation stimulation improves monthly pregnancy rates by increasing the number of mature follicles and oocytes available for fertilization and implantation. Nevertheless, relative to unstimulated IUI cycles, stimulated cycles confer an increased risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS), mainly with the use of gonadotropin injections.

When IUI is used in conjunction with gonadotropins, the response may vary, ranging from no-response (no follicles developed) to hyper-response (more than 4 follicles of >12 mm developed). Amongst hyper-responders, where follicular recruitment is excessive, a decision must be made to either cancel the cycle, or allow the multiple follicles to mature and thus risk the incidence of multiple pregnancy and OHSS.

In cases of hyper-response, treatment with GnRH antagonists like cetrorelix acetate may prevent a premature LH surge and endogenous ovulation in patients undergoing exogenous gonadotropin stimulation. In turn, this may allow the conversion of IUI cycles to IVF cycles (“rescue” IVF) in order to reduce the incidence of multiple pregnancy and OHSS. In this study, we sought to determine whether implantation and pregnancy rates, cost, and OHSS incidence varied between regular hyper-responder IVF cycles (>14 oocytes retrieved) and “rescue” IVF cycles.

Methods

This prospective cohort study was carried out from January 2007 to December 2009 at our private clinic in Montreal, Canada. We prospectively followed 184 couples undergoing stimulated-IUI cycles at our center during the study period. In order to be eligible for IUI treatment, semen parameters must have included at least 5 million sperm/mL and at least 25 % motility of grade A+B according to the 1999 WHO criteria for semen analysis, before the stimulation protocol was carried out [1]. Grade A is defined as sperm with progressive motility; grade B implies a non-linear motility. The ovarian stimulation protocol for IUI consisted of daily gonadotropin injections of 75 IU (37.5 IU in patients with a high ovarian reserve, and 150–225 IU in patients aged 38–40 years), followed by ovulation trigger using subcutaneous injections of 10,000 IU hCG when a leading follicle reached 18 mm size or more. Insemination ensued 36 h later. Serial sonographic and estradiol level monitoring was ensured, and all patients were screened for hyper-response during the stimulation period.

Hyper-response in IUI gonadotropin-stimulated cycles was defined as the development of at least 4 follicles of more than 12 mm. In order to decrease high-order multiple pregnancy, and minimize the incidence of OHSS, these patients were offered the choice of cycle cancellation or conversion to IVF (“rescue” IVF) using the GnRH antagonist cetrorelix acetate. Patients that opted for the “rescue” IVF were then given subcutaneous injection of 0.25 mg of GnRH antagonist when at least 1 follicle reached more than 14 mm in size (flexible GnRH antagonist protocol) [2]. We compared clinical outcomes from these “rescue” IVF cycles with matched, control patients from high-response IVF cycles of the standard long mid-luteal GnRH agonist protocol (14 or more collected oocytes). Our standard long GnRH protocol includes starting the nasal spray buserelin acetate (5 times daily) from day 21 of the cycle. Once down regulation was confirmed by ultrasound and patient serum E2 level (usually after 10–12 days), gonadotropin injections were started in conjunction with the continuous use of the GnRH agonist (3 times daily). Ovulation trigger, in both groups, was then carried out with a subcutaneous injection of 10,000 IU of hCG when 3 follicles were mature (>18 mm), and conventional IVF followed. Embryo transfer was carried out on day 3 in all patients. In patients where only one embryo was available, a single embryo was transferred. On the other hand, in patients older than 40 years, and having had maximum of one quality embryo, 3 embryos were sometimes transferred. Good quality embryos were defined as having between 6 and 10 cells, with less than 20 % fragmentation rate. This criterion was used to cryopreserve surplus embryos. The outcomes considered included implantation rates, biochemical and ongoing clinical

pregnancy rates, cost, ovarian hyperstimulation syndrome (OHSS), as well as the incidence of multiple-order gestations. Ongoing clinical pregnancy was defined as the presence of fetal cardiac activity beyond 10 weeks gestation. We used an unpaired *t*-test with a two-tailed *p*-value to establish statistical significance, which was defined by convention to be established by *p*-values <0.05. No loss to follow-up took place. All cases of IVF with intra-cytoplasmic sperm injection (ICSI), low ovarian reserve, and low and normal response (<14 collected oocytes) were excluded from the study population. This study was approved by the Internal Ethics Board of our institution.

Results

Baseline cohort characteristics of both groups are found in Table 1. Out of 184 patients undergoing stimulated-IUI cycles with gonadotropins, 87 patients developed a hyper-response, demonstrating that our cohort was indeed comprised of high-ovarian reserve patients. Despite an intended 1-to-1 analysis between study and control groups, financial requirements amongst stimulated-IUI groups precluded conversion into the rescue IVF group in a number of cases. The study group was therefore comprised of 20 patients (25 %) from high-response gonadotropin-IUI cycles, which opted to convert to “rescue” IVF. The control group consisted of 157 matched patients from high-response IVF cycles of the standard long mid-luteal GnRH agonist protocol. Mean age and mean day 3 FSH levels were comparable between both groups. Indications for infertility treatment varied considerably between study subjects and controls. Both groups had luteal phase support with 200 mg of intravaginal micronized progesterone thrice daily and 2 mg of 17 β -estradiol orally

thrice daily, starting the day after egg collection. Embryo transfer was carried out on day 3 in all patients (Table 1).

The implantation rate was 25.6 % in the “rescue” IVF group vs. 20.7 % in the control IVF group (*p*=0.0047). Ongoing clinical pregnancy rates per embryo transfer (CPR/ET) were significantly different between both cohorts (45.0 % and 33.6 % in the “rescue” IVF, and the control IVF groups, respectively, *p*<0.0001). The mean duration of stimulation was comparable between both groups: 10.0 days in the study vs. 10.4 days in the control group (*p*=0.6324). The mean dose of gonadotropin used per cycle was higher in the control group, with an average 2664 international units (IU) of follicle stimulation hormone (FSH) compared to 1450 IU of FSH in the “rescue” IVF group. The mean gonadotropin cost, estimated a 0.95\$CAN/IU, was therefore significantly reduced in the study group (*p*<0.0001). The average number of oocytes retrieved and the number of embryos frozen were slightly higher in the control group (*p*=0.008, *p*=0.0017). The total number of embryos transferred (ET) was similar between both groups (*p*=1.0). Both biochemical pregnancy rate (PR) and ongoing clinical pregnancy rate (CPR) were greater with “rescue” IVF (Fig. 1). Incidence of twin gestation was lower in the study group (11.1 vs. 22.0 %). The incidence of severe OHSS in the control group was 5.1 %, while no cases of severe OHSS developed in the “rescue” IVF group (*p*<0.0001) (Table 2).

Discussion

IUI is a common treatment for unexplained infertility and male subfertility. This treatment is often associated with ovulation induction. Indeed, the use of exogenous gonadotropins has revolutionized the treatment of infertility. In

Table 1 Cohort characteristics

	Study group “Rescue” IVF	Control group IVF Hyper-responders	<i>p</i> -value
Number	20	157	–
Average age (range)	32.1 (28–41)	32.8 (25–42)	0.3241
Basal Day 3 FSH	6.1 (4.9–7.2)	5.8 (4.9–7.1)	0.5634
Infertility indication (%)			
Unexplained	30.0	18.2	–
Moderate male factor	35.0	37.7	
Ovulatory	35.0	12.2	
Tubal	0.0	24.2	
Combined	0.0	7.7	
Luteal phase support	Micronized Progesterone 200 mg TID 17 β -estradiol 2 mg TID	Micronized Progesterone 200 mg TID 17 β -estradiol 2 mg TID	– –
Embryo transfer	Day 3	Day 3	–

Fig. 1 Percent incidence of PR/ET, CPR/ET and OHSS by cohort, $p < 0.0001$

patients undergoing IUI, the concomitant use of gonadotropins has been shown to increase the rate of pregnancy in unexplained infertility (OR 2.33, 95 % CI [1.46–3.71]) as well as in male subfertility (OR 1.80, 95 % CI [1.20–2.70]) [3]. Gonadotropin stimulation carries an increased risk of multiple pregnancy and OHSS. Both these complications may be prevented by cycle cancellation, or better yet, by converting IUI-gonadotropin cycles to IVF. Since the advent of GnRH antagonists, the latter can be readily accomplished by provision of the antagonist in order to prevent an LH surge, perform egg retrievals, and proceed to embryo culture and transfer. In this study, we sought to determine whether implantation and pregnancy rates, cost, and OHSS incidence

varied between regular hyper-responder IVF cycles (>14 oocytes retrieved) and “rescue” IVF cycles using a GnRH antagonist in hyper-responder patients undergoing IUI. We show that conversion of high-response gonadotropin-IUI cycles to “rescue” IVF is a cost-effective strategy with relatively minimal morbidity, which provides at least equal or better clinical outcomes than conventional IVF. In addition, implantation and pregnancy rates tend to be higher than those from hyper-responder regular IVF patients.

OHSS The development of OHSS is more frequent in hyper-responder individuals with multiple follicular cysts and high concentration of serum E2 [4]. With the use of “rescue” IVF, the incidence of severe OHSS was relatively low compared to the expected rate, considering the fact that all the study patients were high responders. It has previously been suggested that “rescue” IVF be considered in IUI hyper-responders in which OHSS is imminent, as a measure to reduce its incidence and complication rate [4]. This is in accordance with our findings, where no cases of severe OHSS developed in the study group. A study by Haydardedoglu et al. demonstrates a lower incidence of severe OHSS requiring hospitalization in “rescue” IVF, when compared to conventional IVF as well [5]. This finding may also be explained by the use of the GnRH antagonist in the “rescue” IVF group as compared to the GnRH antagonist use in the control group, which was recently shown

Table 2 Results

	Study group “Rescue” IVF	Control group IVF hyper-responders	<i>p</i> -value
Number	20	157	
Duration of stimulation (days)	10.0 (6–16)	10.4 (7–14)	0.6324
Dose of gonadotropin/cycle	1450 IU (900–4020)	2664 IU (900–6450)	< 0.0001
Mean gonadotropin cost	1,380\$	2,530\$	< 0.0001
Type of gonadotropin			
r-FSH	100 %	75.3 %	–
Mixed	0.0 %	22.2 %	–
hMG	0.0 %	2.5 %	–
# Oocytes	15.2 (8–22)	19.2 (14–36)	0.0088
# Embryos developed	8.7 (1–16)	10.1 (0–31)	0.0634
# Embryos frozen	4.2 (0–13)	5.6 (0–23)	0.0017
#Embryos transferred (ET)	2 (1–3)	2 (1–3)	1.000
Implantation rate (IR)	25.6	20.7	0.0047
Biochemical pregnancy rate (PR)/cycle	65.0	34.4	<0.0001
Biochemical pregnancy rate/transfer (PR/ET)	65.0	37.8	<0.0001
Ongoing clinical pregnancy rate (CPR)/cycle	45.0	30.0	<0.0001
Ongoing clinical pregnancy rate/transfer (CPR/ET)	45.0	32.9	<0.0001
% Severe OHSS	0 %	5.1 %	<0.0001
% Twins	11.1	22.0	<0.0001
% Triplets	0.0	0.0	1.000

in a meta-analysis to confer a lower risk of OHSS [6]. Indeed, we demonstrate that in high ovarian reserve patients, even the minimal type of IVF stimulation used in the IVF rescue group led to retrieve an average of 15.2 oocytes (Table 2). Since the advent of these findings, this type of stimulation is being used at our clinic to stimulate high-ovarian reserve patients because it carries a lower risk of OHSS.

Cost The cost associated with IVF “rescue” is an important issue, which may impede the undertaking of this practice in many centers. Though cycle cancellation can also prevent the occurrence of OHSS, it poses significant financial burdens on the patients, especially in regions and centers where IVF is not funded [7]. In our study, we show that the “rescue” IVF group had, on average, a lower cost per cycle relative to cycle cancellation and conventional IVF. A study comparing “rescue” IVF to conventional IVF in PCO and non-PCO populations, theorizes that lower doses of gonadotropin between the “rescue” IVF group and control groups might be due to ovarian down-regulation in the control groups. This dose difference results in an added cost for hyper-responsive patients on standard IVF programs. Rescue IVF cycles seems therefore to require a milder stimulation protocol that is cost effective compared with the standard strategy for IVF. In addition, the psychological burden of cycle cancellation is a real concern for patients and IUI providers. An added benefit of the practice of “rescue” IVF is that it reduces the emotional stress of couples undergoing treatment that would have otherwise had to wait until subsequent cycles to begin the process anew.

Pregnancy rate With regards to pregnancy rates, studies have shown that IVF may be more effective than stimulated-IUI in achieving a pregnancy [8, 9]. This appears to be independent of whether a GnRH agonist or antagonist protocol is used [9, 10]. For a number of years, a long mid-luteal GnRH agonist protocol for IVF was the standard of care, until research showed the feasibility of IVF with antagonist protocols. GnRH agonist administration causes gonadotropin suppression via pituitary desensitization, after an initial short period of gonadotropin hyper-secretion. This treatment is on the one hand associated with an increased number of ovarian cysts, and on the other hand, with an increased prevalence of side effects, most notably, estrogenic deprivation symptoms. In contrast, GnRH antagonists cause immediate and rapid gonadotropin suppression, by competitive occupancy of the GnRH receptor, and thus intuitively make a more logical choice to use in IVF for the prevention premature LH surges, especially since they reduce the duration of treatment [10]. Therefore, GnRH antagonists could be administered at any time during the early or mid-follicular phase of a treatment cycle to prevent a premature LH surge [10].

Conversion of high-response gonadotropin-IUI cycles to “rescue” IVF could not prevent the prevalence of multiple

pregnancy rates without single or double embryo transfer policies in place [5]. Our study was carried out between 2007 and 2009 in the province of Quebec, Canada where funding of IVF treatments was not included within the provincial coverage plan. Given the costs and the moderate rates of success [11], IVF providers usually transferred two embryos in order to increase the likelihood of at least one successful implantation. This practice carried an increased risk of twin pregnancies, which at the time, stood steadily at 25.6 % in our province. In the hopes to reduce the costs, and the burden on the system that multiple pregnancies carried, the government instituted a plan to fund ART treatment since August 2010. Elective single embryo transfer (eSET) was promoted, and a dramatic decrease in multiple pregnancy rates was rapidly observed thereafter, reaching 3.7 % three months after the provincial funding was instituted [12]. Although eSET strategy yields a lower pregnancy rate than a double embryo transfer (DET) in a fresh IVF cycle, this difference is almost completely overcome by a subsequent frozen single embryo transfer cycle [13]. A major concern remains the incidence of high-order multiple pregnancy stemming from fertility treatments outside IVF. In order to solve this issue, every clinic should implement strict criteria for cycle cancellation, or better yet, conversion to IVF, as was clearly shown in our study group.

A recent meta-analysis demonstrates that elective single embryo transfer results in a higher chance of delivering a term singleton live birth compared with double embryo transfer, and that the multiple pregnancy rate after elective single embryo transfer is comparable with that observed in spontaneous pregnancies [13]. Indeed, the goal of fertility treatment with ovulation induction or stimulation should always be the same: the birth of one, or at most two, babies [14, 15].

This study has a number of limitations. First, though prospective in nature, patients in both control and study groups were not randomized, and primary outcomes did not include live birth rates. The sample size in the study group is small, and thus amenable to bias. The findings are representative of one population at one center, and as such, may not be generalizable. Furthermore, the definition of “hyper-response” in conventional IVF control group was chosen arbitrarily (more than 14 collected oocytes) and may have altered the results of the study had it have been defined otherwise. Finally, double embryo transfers are not commonly carried out at our center anymore. Whether these results could be extrapolated to eSET policy practice is still unknown.

On the other hand, this study has a number of notable strengths. First, this was a prospective study, which recruited patients over a 2-year period. We were able to study almost comparable populations of hyper-response between IUI and regular IVF cohorts by using identical measures for embryo culture, luteal phase support and embryo transfer. This approach reduced significant bias in our

investigation. Furthermore, to the best of our knowledge, ours is the first and only study to compare hyper-response to hyper-response cohorts, and the only study to use a GnRH antagonist in all study group patients, all the while demonstrating its feasibility and success. Finally, the conclusions of this study may reinforce the previously proposed notion that IVF should be the first line treatment in unexplained infertility and male subfertility with a good ovulation stimulation response [8], because single embryo transfers may confer an overall lower cost and similar results to conventional algorithms [5].

All in all, our study demonstrates that among hyper-responders, “rescue” IVF provides at least equal clinical outcomes than regular IVF, with less cost, and lowered incidence of OHSS. This practice is efficacious, secure, and carries minimal morbidity relative to stimulated IUI. For women with a high ovarian reserve undergoing IVF stimulation, this protocol might be the standard of care. Well-conducted randomized control trials are required to validate these findings.

Conflict of interest The authors disclose no conflict of interest.

Funding The authors have no funding to declare.

References

1. Murray KS et al. The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility. *Fertil Steril*. 2012;98(6):1428–31.
2. Al-Inany H et al. Optimizing GnRH antagonist administration: meta-analysis of fixed versus flexible protocol. *Reprod Biomed Online*. 2005;10(5):567–70.
3. Attia AM et al. Gonadotrophins for idiopathic male factor subfertility. *Cochrane Database Syst Rev*. 2007;4, CD005071.
4. Many A et al. Pregnancy rate in IVF rescue in high responders to human menopausal gonadotropin. *J Assist Reprod Genet*. 1999;16(10):520–2.
5. Haydardedeoglu B et al. 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(1):137–42.
6. Al-Inany HG et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev*. 2011;5, CD001750.
7. Zhong Y et al. The efficacy of conversion from IUI to IVF-ET in infertility patients with hyper-response to ovulation induction: a retrospective study. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2012;156(2):159–63.
8. Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. *Cochrane Database Syst Rev*. 2012;4, CD003357.
9. Reindollar RH et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril*. 2010;94(3):888–99.
10. Huime JA, Homburg R, Lambalk CB. Are GnRH antagonists comparable to agonists for use in IVF? *Hum Reprod*. 2007;22(11):2805–13.
11. Olufowobi O et al. Role of rescue IVF-ET treatment in the management of high response in stimulated IUI cycles. *J Obstet Gynaecol*. 2005;25(2):166–8.
12. Bissonnette F et al. Working to eliminate multiple pregnancies: a success story in Quebec. *Reprod Biomed Online*. 2011;23(4):500–4.
13. McLernon DJ et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ*. 2010;341:c6945.
14. Dickey RP. Strategies to reduce multiple pregnancies due to ovulation stimulation. *Fertil Steril*. 2009;91(1):1–17.
15. Pandian Z et al. Number of embryos for transfer after IVF and ICSI: a Cochrane review. *Hum Reprod*. 2005;20(10):2681–7.