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ORIGINAL ARTICLE *Infertility*

Reproductive outcome of fresh or frozen–thawed embryo transfer is similar in high-risk patients for ovarian hyperstimulation syndrome using GnRH agonist for final oocyte maturation and intensive luteal support

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BACKGROUND: Triggering ovulation by GnRH agonist (GnRHa) in GnRH antagonist IVF protocols coupled with adequate luteal phase support has recently been suggested as a means to prevent ovarian hyperstimulation syndrome (OHSS). Our objective was to examine the outcome of fresh embryo transfer (f-ET) after triggering ovulation by GnRHa and providing intensive luteal phase supplementation, compared with that of the next first frozen–thawed embryo transfer (ft-ET) after cycles with the same protocol and cryopreservation of all the embryos.

METHODS: We performed a cohort study at a university-based IVF clinic. The study population was patients at high risk for OHSS. A daily dose of 50 mg i.m. progesterone in oil and 6 mg of oral 17-β-estradiol initiated on oocyte retrieval day in the f-ET group ($n = 70$). In the ft-ET group ($n = 40$) the embryos were cryopreserved and transferred in the next cycle.

RESULTS: The live birth rate per f-ET was 27.1 versus 20% in the ft-ET groups [$P = 0.4$; rate ratio = 1.36 (0.65–2.81)]. The implantation, pregnancy and spontaneous abortion rates were comparable in both groups. None of the patients developed OHSS.

CONCLUSIONS: In this observational cohort study, we showed that triggering ovulation with GnRHa and intensive luteal phase support is a promising new modality to prevent OHSS without the cost of cycle cancellation, ET deferral and reduced clinical pregnancy rates. Confirmation of these findings by RCTs is now required.

Key words: ovarian hyperstimulation syndrome / GnRH agonist / embryo transfer / luteal support / frozen–thawed embryo transfer

Introduction

Prevention of ovarian hyperstimulation syndrome (OHSS) in high-risk populations has become a major goal in the research of controlled ovarian stimulation (COS) in IVF programmes. Withholding hCG and cycle cancellation is considered the safest option but carries adverse emotional and financial implications. Withholding treatment for several days (coasting) has been shown to diminish the incidence and severity of OHSS without compromising pregnancy rates (Garcia-Velasco *et al.*, 2006). Others have shown a less favourable clinical outcome with coasting owing to lower yield of retrieved oocytes, and decreased implantation and pregnancy rates (Delvigne and Rozenberg, 2002, 2003; Moreno *et al.*, 2004). Recently, the pregnancy outcome using GnRH agonist (GnRHa) triggering for final oocyte maturation was claimed to be superior to that of coasting in patients at high risk for OHSS (DiLuigi *et al.*, 2010). Freezing all of the embryos and refraining from fresh embryo transfer (f-ET) has also been suggested as an option to prevent OHSS (Queenan, 2000). Some

authors have shown that the process of freezing and thawing might carry the toll of impaired embryo survival after thawing and reduced pregnancy rates (Huddleston et al., 2008; Manzanares et al., 2010). A recent observational trial showed that oocyte vitrification after GnRHa triggering is another highly attractive, safe and efficient alternative for preventing OHSS (Herrero et al., 2011). Of note is that freezing all the embryos and deferring from f-ET will not prevent the early disease which can be just as life threatening as the late-onset OHSS (Tang and Balen, 2009). Yet, none of the methods that eventually use hCG for ovulation induction have been shown to completely eliminate the risk of the syndrome (DiLuigi et al., 2010).

The ovulation-inducing agent commonly used so far in COS cycles is hCG. Given its significantly longer half-life (30 h) than the endogenous LH surge, hCG administration results in a prolonged luteotrophic effect, which is characterized by the development of multiple corpora lutea and supraphysiologic levels of vascular endothelial growth factor (VEGF; McClure et al., 1994). The sustained luteotrophic effect of VEGF may be pivotal to the development of OHSS via the enhancement of capillary leak (Lesterhuis et al., 2009).

Along with the introduction of GnRH antagonist protocols to prevent premature LH surge in COS cycles, triggering of ovulation with a single dose of GnRHa became an alternative to hCG for final egg maturation (Gonen et al., 1990; Itskovitz et al., 1991; Itskovitz-Eldor et al., 2000; Fauser et al., 2002; Orvieto et al., 2006; Bodri et al., 2009). Previous trials described the beneficial effect of the GnRHa approach that virtually eliminated OHSS in high-risk patients at the cost of reduced pregnancy rates (Humaidan et al., 2005). The GnRHa protocol was associated with comparable numbers of retrieved oocytes but lower ongoing pregnancy rates, compared with hCG (Griesinger et al., 2006). The unfavorable outcome of f-ET with this approach had led clinicians to favor cryopreservation of all the embryos after GnRHa trigger of ovulation in GnRH antagonist cycles and frozen–thawed ET (ft-ET) in a future cycle (Griesinger et al., 2007a,b; Griesinger et al., 2011). The low implantation rate of embryos after GnRHa had been attributed to inadequate endometrial receptivity related to luteal phase insufficiency (Segal and Casper, 1992), reflected by lower levels of steroidal and non-steroidal hormones (Nevo et al., 2003).

Supporting this hypothesis, an adequate luteal phase support with either repeated low dose hCG or intensive estradiol (E_2) and progesterone administration from the time of oocyte retrieval yielded a favourable outcome after f-ET (Humaidan et al., 2006, 2010; Engmann et al., 2008). A recent review investigating the experience with the new protocol concluded that GnRHa triggering is a valid alternative to hCG, resulting in the prevention of OHSS (Humaidan et al., 2011).

To our knowledge there are no studies to date that have compared outcomes using GnRHa to trigger ovulation with f-ET to those of the same GnRH trigger with transfer of ft-ET after endometrial preparation in the following cycle.

The aim of the present study was to compare the live birth rate of these two protocols designed to prevent OHSS in high-risk patients.

Materials and Methods

Study design and participants

We conducted an observational prospective cohort study with a retrospective historical control in a total of 110 patients at high risk for OHSS undergoing ovulation triggering with GnRHa in GnRH antagonist cycles. In 40 patients, from January 2006 to March 2008, all embryos were cryopreserved (ft-ET group). Following the publication by Engmann et al. (2008), our group endorsed their protocol and transferred embryos with intense luteal support. We followed 70 patients from April 2008 to March 2010; all patients had fresh embryos transferred according to this protocol (f-ET group). Four patients underwent 2 GnRHa final oocyte maturation cycles during the study period, and only their first cycle was considered for analysis.

The inclusion criteria were based on at least one of the following: young age <22 years, lean (BMI < 19 kg/m^2), diagnosis of polycystic ovary syndrome according to the Rotterdam criteria (2004) or history of high response during a previous COS cycle, defined as occurrence of at least one of the following: E_2 levels $>12\,000$ pmol/l on the day of hCG administration, 20 follicles with a mean diameter of at least 10 mm, in addition to the leading follicles on the day of hCG administration, cycle cancellation in the past related to high response and development of moderate or severe OHSS after hCG administration.

Triggering ovulation with GnRHa was used when E2 levels exceeded 10 000 pmol/l or more than 8 follicles larger than 16 mm on ovulation induction day were observed.

Treatment protocol

All patients underwent ovarian stimulation with recombinant FSH (rFSH, Puregon; Schering-Plough, Oss, The Netherlands or Gonal-F, MerckSerono, Geneva, Switzerland) starting on the third day of the menstrual cycle. Medication and protocol choice were based on physician preference. Starting dose of FSH ranged from 100 to 225 IU daily. Medication dose was adjusted on the basis of individual response. hMG (Menogon or Menopur, Ferring GmbH, St Prex, Switzerland) or recombinant LH (Luveris, MerckSerono, Geneva, Switzerland) were administered when the patients were given GnRH antagonist (Cetrotide, MerckSerono, Geneva, Switzerland or Orgalutran, Schering-Plough, Oss, The Netherlands) usually when follicles reached 14 mm in diameter.

All patients were given 0.2 mg of the GnRHa Triptorelin (Decapeptyl, Ferring GmbH. St Prex, Switzerland) to induce ovulation 36 h prior to the oocyte retrieval procedure.

In the f-ET group, luteal phase support included a daily dose of 50 mg i.m. progesterone in oil (Gestone, Nordic Pharma, Ashton-under-lyne, UK,) and oral administration of 6 mg of E_2 (Estrofem, Novo Nordisk A/S, Bagsverd, Denmark) initiated on the day of oocyte retrieval until 10 weeks gestation. Embryos were graded according to the criteria described by Cummins et al. (1986). ET was carried out 2–3 days after fertilization.

The ft-ET group underwent ovarian stimulation with a similar short GnRH antagonist protocol and ovulation induction by GnRHa (0.2 mg of Triptorelin), without f-ET. All the embryos in this group were cryopreserved on Day 3 after fertilization. The transfer of thawed embryos was carried out on the first next cycle after endometrial sequential preparation with a daily dose of orally administered 6 mg of E_2 (Estrofem, Novo Nordisk A/S, Bagsverd, Denmark) followed by 400 mg bid of vaginal micronized progesterone (Uterogestan, Besins International, France). The number of fresh or frozen–thawed embryos transferred in each cycle was based on the preference of the physician and treated couple. The number of transferred embryos was in accordance with the policy declared by the Israeli Fertility Association (IFA) position paper (IFA position paper no. 201, March 2010). When pregnancy was achieved, E_2 and progesterone supplementation was continued until 10 weeks gestation.

Table I Clinical characteristics and cycle parameters of participants in study of outcome of f-ET after GnRHa with luteal phase supplementation compared with ft-ET.

	f-ET (n = 70), mean ± std; median (25th–75th percentile)	ft-ET (n = 40), mean ± std; median (25th–75th percentile)	P-value
Age (years)	30.04 ± 6.4; 29.5 (25–34)	30.03 ± 6.4; 29 (24.5–34.5)	0.98[a]
BMI (kg/m^2)	25.7 ± 6.1; 25 (21.3–27.8)	25.5 ± 6.5; 23.4 (20.5–27)	0.91[a]
Percentage of patients with PCOS	15.4%	32.4%	0.05[b]
Percentage of nulliparous patients	75%	85.3%	0.48[b]
Day 3 FSH (IU)	6 ± 2; 5.7 (4.8–7)	6.2 ± 2.9; 5.7 (4.7–7)	0.75[a]
Peak estradiol (pmol/l)	11 427 ± 3206; 11 189 (9680–13 785)	10 235 ± 4223; 10 504 (6029–13 429)	0.14[a]
Stimulation length (days)	9.76 ± 1.8; 10 (8–11)	10.8 ± 4; 10 (9–12)	0.28[a]
Total recombinant FSH (IU)	1670 ± 653; 1562 (1225–1950)	1654 ± 765; 1500 (1087–1912)	0.91[a]
Estradiol at GnRHa administration (pmol/l)	11 247 ± 3174; 11 057 (9456–13 660)	9668 ± 4096; 10 071 (5626–13013)	0.03[a]
Cancellation rate (%)	0	0	
No. of retrieved oocytes	18.3 ± 7.1; 17 (13–23)	20.9 ± 9.5; 20.5 (13–23)	0.16[c]
No. of matured oocytes	14.2 ± 6.1; 12 (10–19)	17.5 ± 8.3; 16.5 (11–24)	0.04[c]
No. of fertilized oocytes (2 Pronuclei)	11 ± 5; 10 (7–15)	14.7 ± 7.7; 14 (9–19.5)	0.02[c]
Fertilization rate (%)	78 ± 17; 79 (70–90)	88 ± 20; 90 (85–100)	0.002[c]
No. of embryos per cycle	9.8 ± 4.8; 8 (6–12)	12.6 ± 6.5; 11 (8–16)	0.02[c]
No. of good-quality embryos per cycle	6.4 ± 4.5; 6 (3–9)	7.7 ± 5; 8 (3–9)	0.07[c]
No. of embryos per ET	2 ± 0.56; 2 (2–2)	2.3 ± 0.97; 2 (2–3)	0.12[c]
No. of good-quality embryos per ET	1.7 ± 0.8; 2 (1–2)	1.7 ± 0.9; 2 (1–2)	0.55[c]

PCOS, polycystic ovary syndrome; f-ET, fresh embryo transfer; ft-ET, frozen–thawed embryo transfer.
[a]Student's t–test.
[b]χ^2- test.
[c]Wilcoxon rank sum test.

Outcome measures

The primary study outcome was live birth rate. Secondary outcomes were implantation, pregnancy and OHSS rates. Live birth rate was defined as delivery of a live newborn. Multiple pregnancy cases were included as one live birth. Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per patient. A biochemical pregnancy was defined as a pregnancy diagnosed by the detection of β-hCG in the serum. Pregnancy rate was defined as the number of patients with positive serum β-hCG levels, drawn 14 days after oocyte retrieval out of the whole group. Clinical pregnancy was defined as a gestational sac shown by transvaginal sonogram.

Spontaneous abortion rate was defined as the percentage of gestational sacs proven by ultrasonography that did not develop beyond the 20th week of pregnancy out of the total number of clinical pregnancies. These criteria are in accordance with the revised glossary of assisted reproduction techniques (Zegers-Hochschild *et al.*, 2006).

Statistical methods

Mean, SD, median, 25th, 75th percentile and percentages are presented where appropriate. Wilcoxon rank sum test was used to compare mean ranks between the control and study groups for the following parameters: number of retrieved oocytes, matured oocytes, fertilized oocytes (2PN), embryos per cycle, good-quality embryos per cycle, embryos per ET and good-quality embryos per ET. The Student's t-test was used to compare means of continuous variables (age, BMI, Day 3 FSH, peak E2, total rFSH, E_2 at GnRHa administration and implantation rate). Chi square test was used for categorical outcomes (PCOS, nulliparous patients). Rate difference (RD), rate ratio (RR) and 95% confidence intervals (CIs) were calculated.

Sample size calculations were based on the assumptions of a pregnancy rate of 7% for f-ET (Griesinger *et al.*, 2006) and 40% for ft-ET (based on our own data) with alpha of 5 and 80% power. Based on these assumptions, 35 patients were needed in each group. All P-values are two-sided, and P-values <0.05 were considered to be statistically significant. Statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Clinical and cycles characteristics of the two groups are presented in Table I. The mean ± SD level of serum E_2 levels on day of GnRHa were 11 247 ± 3174 and 9668 ± 4096 pmol/l in the f-Et and ft-ET groups, respectively ($P = 0.03$). The number of ova retrieved was similar in both groups ($P = 0.16$); the ft-ET group had a higher number of metaphase II oocytes (14.2 ± 6.1 versus 17.5 ± 8.3, $P = 0.04$). A difference in the fertilization rate ($P = 0.002$) and the number of developing embryos ($P = 0.02$) was also found between the groups.

None of the cycles in the f-ET group was cancelled and all the patients followed the treatment protocol of i.m. progesterone and oral estrogen. In the ft-ET group all patients had at least one good-quality embryo for transfer after the thawing procedure. The mean survival rate of thawed embryos was 79% ± 23. The number of fresh embryos transferred per cycle in the f-ET group was comparable

Table II Clinical outcomes following f-ET and ft-ET.

	Study (f-ET) group ($n = 70$)	Control (ft-ET) group ($n = 40$)	RD (95% CI)	RR (95% CI)	*P*-value[a]
Mean implantation rate	24.2 ± 34%	23 ± 36%	−1.2% (−15 to 13)		0.8
Pregnancy rate	34 (48%)	21 (52%)	−4% (−25 to 17)	0.93 (0.63–1.35)	0.69
Clinical pregnancy rate	26 (37%)	14 (35%)	2% (−18 to 23)	1.06 (0.63–1.79)	0.8
Spontaneous abortion rate	7 (10%)	6 (15%)	−5% (−20 to 10)	0.67 (0.24–1.85)	0.43
Live birth rate	19 (27.1%)	8 (20%)	7.1% (−11 to 25)	1.36 (0.65–2.81)	0.4
Multiple pregnancy rate	4 (5.7%)	3 (7.5%)	−1.8% (−14 to 10)	0.76 (0.18–3.23)	0.7
Patients with surplus cryopreserved embryos	67 (95.7%)	38 (95%)	0.7% (−9.5 to 11)	1.008 (0.92–1.1)	0.9
OHSS occurrence (95% CI for proportion)	0 (0–0.05)	0 (0–0.96)	NA	NA	

OHSS, ovarian hyperstimulation syndrome; CI, confidence interval.
[a]χ^2-test for categorical outcomes and t test for implantation rate.

to that of frozen–thawed embryos transferred to the patients in the ft-ET group (2 ± 0.56 versus 2.3 ± 0.97, $P = 0.12$).

The clinical outcomes are presented in Table II. Comparable live birth rate was found in the two groups; 27.1% in the f-ET and 20% in the ft-ET group [$P = 0.4$, RR = 1.36 (0.65–2.81)]. Mean Implantation rate was similar in the two groups ($P = 0.8$) as were the pregnancy rate ($P = 0.69$) and the multiple pregnancy rate ($P = 0.7$). The clinical pregnancy rate in the f-ET group was similar to that of all hCG-ovulation induced IVF cycles conducted over the study period in our IVF unit (data not shown). Spontaneous abortion rate was 10% in the f-ET and 15% in the ft-ET ($P = 0.43$), RR = 0.67 (0.24–1.85). One ectopic pregnancy occurred in the f-ET and none in the ft-ET group. OHSS did not occur in any of the patients in both groups.

Discussion

Our study shows that OHSS is avoided, even in high-risk patients, using the GnRHa as ovulation trigger in GnRH antagonist-based cycles. We also show that acceptable clinical pregnancy and live birth rates can be achieved by either ft-ET after cryopreservation of all embryos, or f-ET after GnRHa trigger, provided that adequate luteal phase support is administered. Moreover, the spontaneous abortion rate with this regimen is in accordance and somewhat less than the rate of pregnancy loss published by the American Society for Reproductive Medicine (ASRM/SART registry, 2007). These results support our null hypothesis assuming that the clinical outcomes of GnRHa ovulation induction and f-ET are as good as using the same protocol and freezing all embryos for utilization in future ft-ET cycles.

The current study corroborates previous reports advocating that GnRHa trigger of ovulation holds the promise of avoiding OHSS without compromising cycle outcome (Acevedo *et al.*, 2006; Engmann *et al.*, 2008; Bodri *et al.*, 2009, 2010; Hernandez *et al.*, 2009; Galindo *et al.*, 2009; Sismanoglu *et al.*, 2009; DiLuigi *et al.*, 2010; Humaidan *et al.*, 2010; Manzanares *et al.*, 2010). The use of this protocol allows the treatment of patients at high risk for OHSS without the need of taking any preventive measures, such as cycle cancellation, coasting, embryo freezing or deferral of ET to avoid OHSS, and yet attaining favourable implantation and pregnancy rates in the current cycle.

Moreover, we used a rather conservative approach of GnRHa triggering compared with the known literature about high responders (Asch *et al.*, 1991; Morris *et al.*, 1995), and used this protocol even with relatively low levels of E_2 (10 000–12 500 pmol/l) at ovulation-induction day. This conservative approach allowed us to draw a conclusion for women with normal to high ovarian response.

GnRHa trigger and f-ET have not gained wide acceptance in previous years, most likely because of poor initial results reported by some studies (Humaidan *et al.*, 2005; Kolibianakis *et al.*, 2005). These studies were using conventional doses of micronized progesterone for luteal phase support that had been found to be inadequate in GnRHa trigger cycles. Moreover, a recent Cochrane review reported that, along with a significant reduction in the OHSS rate when using the GnRHa to trigger ovulation, the live birth and ongoing pregnancy rates were lower compared with protocols using hCG as the ovulation trigger (Youssef *et al.*, 2010). Their review addressed the luteal support without any consideration of the type of progesterone used. In fact, the only two studies (Fauser *et al.*, 2002; Babayof *et al.*, 2006) that reported use of i.m. oil-based progesterone after GnRHa showed favourable pregnancy and live birth rates. All other studies used micronized progesterone in regular doses or no progesterone supplementation at all. In their conclusions Youssef *et al.* (2010) stated that an exception to their unfavorable conclusions could be made for patients at high risk of OHSS.

Our regimen, based on Engmann *et al.* (2008), requires administration of an intensive luteal phase support with estrogen and progesterone, owing to the profound luteolysis caused by the GnRHa. It has been shown that triggering ovulation with GnRHa and rescuing the luteal phase with hCG (1500 IU) on the day of oocyte retrieval normalized the pregnancy and delivery rates to that achieved by protocols using hCG to trigger ovulation, with no increase in OHSS prevalence (Humaidan *et al.*, 2010). However, using hCG to rescue the luteal phase might increase the risk of late-onset OHSS (Castillo *et al.*, 2010). A single report of late-onset severe OHSS using the GnRHa protocol along with micronized progesterone was found to be controversial, and the symptoms of OHSS in this case were attributed to subacute i.p. haemorrhage occurring at oocyte retrieval (Griesinger

et al., 2011). We believe that the target of the progesterone administered for luteal support in this protocol is mainly the developing embryo and decidua rather than the corpora lutea (Lesterhuis et al., 2009); therefore we hypothesize that late-onset OHSS with this protocol is highly unlikely.

Owing to its luteolytic effect, the GnRHa trigger is associated with an altered luteal hormonal milieu and a significantly shortened luteal phase (Yding Andersen et al., 1993). Therefore, adequate and early luteal phase support with E_2 and progesterone is vital to achieve favourable pregnancy rates. The use of i.m. administration of progesterone has been shown in a prospective RCT to secure good reproductive outcome (Engmann et al., 2008). By improving the suboptimal luteal phase, this GnRHa protocol has also been shown to be superior to coasting with respect to implantation, pregnancy and ongoing pregnancy rates per ET (DiLuigi et al., 2010).

The total elimination of OHSS with this protocol in a high-risk group of patients with high E_2 levels, suggests that repeated blood hormone measurements during COS and on the day of ovulation induction may be unnecessary. Further data on this issue may enable reducing the cost and tight surveillance of IVF treatments in general and in patients at high risk of OHSS in particular.

The relatively high pregnancy rate achieved with the GnRHa protocol (with or without embryo cryopreservation) probably reflects the increased oocyte yield and quality in these young and highly responsive patients.

In face of the cost of oocyte and embryo freezing and the risk to embryo survival during the thawing process, we recommend adopting this approach and forestall unnecessary embryo freezing. Using our f-ET protocol and avoiding delayed ET might have an encouraging psychological impact on the patients.

The study design of a cohort observational study with historical control has limitations. The two groups were treated in sequential time periods. One may suspect a selection bias of the cases for ovulation induction by GnRH. On the other hand, since we changed the policy based on Engman's protocol (Engmann et al., 2008), all eligible women had f-ET rather than ft-ET.

In order to consider GnRHa trigger and intensive luteal phase support as a legitimate tool in IVF treatments for high responders, a prospective RCT is required. Yet, the results of this study are reassuring to patients who wish to have their embryo transferred in the same treatment cycle, without the risk of OHSS. The chief inconvenience of this treatment protocol is the daily i.m. progesterone injections. Further studies are needed in order to verify our data and conclusions as a solid, evidence-based protocol and to find out whether other better tolerated methods of delivering high dose progesterone could yield a favourable reproductive outcome as well.

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Authors' roles

T.I., S.K., R.H.-K.: Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published. F.L., B.Y.: Acquisition of data, analysis and interpretation of data and final approval of the version to be published. A.H.: Substantial contributions to conception and design, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published.

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Conflict of interest

None declared.

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