J Assist Reprod Genet (2008) 25:515–521
DOI 10.1007/s10815-008-9266-6

ASSISTED REPRODUCTION

Increased gonadotrophin stimulation does not improve IVF outcomes in patients with predicted poor ovarian reserve

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Received: 13 May 2008 / Accepted: 9 October 2008 / Published online: 30 October 2008

Abstract

Purpose This retrospective study was carried out to evaluate whether increasing the starting dose of FSH stimulation above the standard dose of 150 IU/day in patients with low predicted ovarian reserve can improve IVF outcomes.

Method A total of 122 women aged less than 36 years in their first cycle of IVF were identified as having likely low ovarian reserve based on a serum AMH measurement below 14 pmol/l. Thirty five women were administered the standard dose of 150 IU/day FSH, while the remaining 87 received a higher starting dose (200–300 IU/day FSH). There were no significant differences in age, BMI, antral follicle count, serum AMH, FSH or aetiology of infertility between the two dose groups.

Results No significant improvement in oocyte and embryo yield or pregnancy rates was observed following an upward adjustment of FSH starting dose. While increasing the dose of FSH above 150 IU/day did not produce any adverse events such as OHSS, it did consume an extra 1,100 IU of FSH per IVF cycle.

Conclusion The upward FSH dose adjustment in anticipation of low ovarian reserve can not be advocated as it is both expensive and of no proven clinical value.

Capsule Upward FSH dose adjustment in anticipation of diminished ovarian reserve predicted by low serum anti-müllerian hormone levels does not improve IVF outcomes.

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Keywords Anti-Müllerian hormone · Predicted poor ovarian reserve controlled ovarian hyper-stimulation · FSH dose adjustment · IVF

Introduction

During IVF treatment the primary aim of controlled ovarian hyper-stimulation (COH) using gonadotrophin injections is to stimulate the development of several mature oocytes, rather than a solitary oocyte that would develop in an unstimulated "natural" cycle. Because of the considerable natural attrition that occurs during IVF treatment (failed fertilization, poor embryo development), this COH approach maximizes the chances of producing good quality embryos available for transfer or cryopreservation, thereby ultimately boosting pregnancy rates. Previous studies have suggested that an ideal IVF response is approximately 5–15 mature eggs. The production of less than five oocytes has been shown to significantly reduce a woman's chances of a live birth [1, 2] while the development of more than 15 oocytes places her at considerable risk of potentially dangerous Ovarian Hyper-Stimulation Syndrome (OHSS).

Three decades after the birth of the first IVF baby, poor response to ovarian hyperstimulation still remains a frustrating limiting factor for IVF programs throughout the developed world. The current trend for women to delay pregnancy until their 30's has created a situation where many IVF patients have diminished ovarian reserve limiting their response to COH and ultimately their chances of pregnancy. The "standard" approach to

predicting a patient's response to COH has been based on age and early follicular phase FSH levels. Good prognosis patients (age <36 years, normal FSH level) are generally started on 150 IU/day of FSH, while women with probable diminished ovarian reserve (age >36 years, elevated FSH, one ovary) are started on 200–300 IU/day of FSH [3]. The starting dose of FSH used in any subsequent cycle is then adjusted according to the individual patient's response in their first cycle. Unfortunately this approach is less than ideal since it results in an inadequate response in about 50% of patients and an excessive response in 2–5% of cycles [4, 5].

Tests that are sensitive enough to accurately quantify ovarian reserve have the potential to help clinicians individualize the starting dose of rFSH used in a first cycle of IVF, thereby potentially improving the efficacy and safety of treatment. Previous studies have shown that maternal age, antral follicle count, ovarian volume, ovarian doppler score and smoking status can help to predict a patient's response to COH [3]. A prospective randomized control trial that compared a standard starting dose of gonadotrophins in the first cycle of IVF (150 IU/day FSH) with an individualized starting dose (100–250 IU/day) based on such a predictive normogram (age, antral follicle count, ovary volume , Doppler score and smoking status) confirmed that an individualized starting dose was more effective at achieving an "ideal response" (5–14 oocytes) than a standard starting dose (77.1% v 65.6% ideal response, $p < 0.05$). While some studies have shown a positive benefit from increasing the starting dose of gonadotrophin [3, 5], many others have not shown a benefit [4, 23, 26]. Therefore, it is presently uncertain if upward adjustment of gonadotrophin starting dose has any clinical value.

Recently serum Anti-Müllerian Hormone (AMH) has become an increasingly popular method for assessment of ovarian reserve, making it a potentially useful determinant for starting dose of gonadotrophin. AMH is a glycoprotein produced by the granulosa cells within pre-antral and early antral follicles [6]. Serum AMH levels closely reflect the size of the growing cohort of small follicles which are sensitive to gonadotrophin stimulation, making it an ideal predictor of ovarian response during COH. In 2002, de Vet et al published a landmark paper that reported a 38% decline in AMH levels over a mean period of only 2.6 years in a group of young ovulatory women. This large decline in AMH over a relatively short period of time was not accompanied by any significant change in antral follicle count, serum FSH or inhibin B levels, suggesting that AMH is the most sensitive maker of ovarian reserve [7]. Since then several reports have confirmed that serum AMH is the most sensitive predictor of ovarian response to COH compared to more traditional markers such as age, FSH, inhibin B, antral follicle count and ovary volume [8, 9]. Several research groups have confirmed that low serum AMH levels are predictive of a poor response to COH [10–21]. Therefore, it is possible that by using serum AMH assessment of ovarian reserve, clinicians may be able to identify women with early diminished reserve and place them on a maximal dose of FSH in their first cycle of IVF, thereby maximizing the number of retrieved oocytes without placing patients at risk of OHSS. Such an approach is more likely to be successful than adjusting the starting dose of FSH based on late markers of diminished ovarian reserve (high basal FSH, low ovary volume), as the ovary is often resistant to even maximal stimulation at this late stage.

The aim of this study was to determine if upward adjustment of the starting dose of rFSH (200–300 IU/day) in the first cycle of IVF in women with predicted low ovarian reserve, as assessed by serum AMH measurement, will result in a superior IVF outcome than the standard approach of starting on 150 IU/day of rFSH.

Material and methods

A total of 122 patients attending a private reproductive medicine unit (Repromed, Adelaide, South Australia) between February 2005 and May 2007 were included in this retrospective study. The inclusion criteria were: (1) maternal age less than 36 years, (2) first cycle of IVF treatment and (3) predicted diminished ovarian reserve based on a low serum AMH level (<14 pmol/l). A previous study within the author's unit had reported that serum AMH level below14 pmol/l predicted a poor response to COH (<4 oocytes) with a sensitivity and specificity of 73% [19]. Exclusion criteria were (1) repeat cycles of IVF, (2) donor oocyte cycles and (3) evidence of advanced loss of ovarian reserve (early follicular phase FSH >10 IU/l).

The standard approach to COH used in the author's unit was to start all good prognosis patients (maternal age <36 years, early follicular FSH <10 IU/L) on a starting dose of 150 IU/day of rFSH in their first cycle of IVF. Patients aged >36 years of age or those with elevated FSH levels were placed on a higher starting dose of rFSH (200–300 IU/day). However, following research within the author's own unit showing serum AMH to accurately predict a poor response to COH [19], several clinicians began to upwardly adjust the starting dose of rFSH to 200–300 IU/day in the first cycle of IVF in any woman with an AMH <14 pmol/l. The remaining clinicians adhered to a "per protocol" approach of starting all women under 36 years in their first cycle of IVF on a dose of 150 IU/day rFSH as it was their professional opinion that stimulation protocols should not be modified until evidence of safety and benefit became available. The two different clinical practices allowed us to

retrospectively analyse the effectiveness of dose adjustments in low ovarian reserve patients.

The exclusion of older women (>36 years of age) from this retrospective study was made for two reasons. Firstly, previous studies have shown that the ceiling for maximal effect of gonadotrophin stimulation is approximately 200–300 IU/day [22, 23]. Only upward adjustments of the starting dose below this 200 IU/day ceiling have been shown to improve IVF oocyte yields [3, 23–27]. As women 36 years and older were routinely placed on 200–300 IU/day rFSH, it was unlikely that this group would gain further from an upward dose adjustment. Secondly, previous studies had shown that only women aged less than 36 years, not older women, produced more oocytes during COH if their starting dose of FSH stimulation was increased beyond 150 IU/day [26, 28].

Antral follicle counts and serum FSH, LH, oestradiol and AMH measurements were taken on day 3–5 of a spontaneous menstrual cycle within 12 months of the index IVF cycle. Serum samples were separated within 1h of collection and frozen at −20°C until assayed. All hormone measurements, with the exception of AMH (see below), were conducted using the automated ADVIA Centaur chemiluminescent immunoassay system obtained from Bayer Australia (Pymble, NSW, Australia). The FSH assay, calibrated against the WHO second International Standard, IS 94/632, has an analytical sensitivity of 0.3 IU/L with inter- and intra-assay coefficients of variation (CVs) of <4.0%. Serum AMH levels were measured using the Immunotech high-sensitivity immuno-enzymetric assay (Beckman Coulter, Marseille, France). The analytical sensitivity of this assay is 0.7pmol/L. Inter- and intra-assay CVs were ≤14.2% and ≤12.3%, respectively.

The IVF protocol used in this study was the traditional long down-regulation cycle. Briefly, this consisted of commencing pituitary down regulation in the mid-luteal phase of the preceding menstrual cycle by the use of nafarelin acetate (Synarel-Pharmacia, Rydalmere, NSW, and Australia). After confirmation of pituitary desensitization usually after a minimum of 14 days of treatment, recombinant FSH (Puregon-Organon, Lane Cove, NSW or Gonal F-Serono, Frenchs Forrest, NSW, Australia) was commenced. Following 5–7 days of gonadotrophin stimulation, a pelvic ultrasound and oestradiol measurement was taken to assess ovarian response. Patients were scheduled with a trigger injection of 5,000 IU of hCG (Profasi, Serono, Frenchs Forrest, NSW, Australia) once two or more lead follicles were 18–20mm in size. Trans-vaginal oocyte retrieval was performed 36h later under light sedation. Insemination of oocytes (routine insemination or ICSI, depending on sperm quality) was performed on the day of oocyte retrieval and fertilization then verified 16h later. Embryos were graded according to the usual morphological criteria and transferred 2–5 days after oocyte retrieval under ultrasound guidance. Single embryo transfer was standard practice in all women under 36 years of age in their first cycle of IVF. Luteal support was provided with vaginal progesterone (Crinone, Serono, Frenchs Forrest, NSW, Australia) supplemented by one 500 IU dose of hCG on day 6 post retrieval. Biochemical pregnancy was defined as a serum βHCG >40 IU/l on day 16 post oocyte retrieval and a clinical pregnancy as the ultrasound observation of fetal heart movements at 7–8 weeks of gestation.

Institutional ethics committee approval (Women's and Children's Hospital, North Adelaide, Australia) was granted to conduct this retrospective audit.

All statistical analysis was performed using the Sigma Stat 2.03 statistical package. The baseline characteristics and embryo quality data of the two treatment groups were analyzed using the Chi Square statistic. The remaining data was analyzed using the student's t test with all results expressed as mean ± standard error of mean values.

Results

A total of 122 patients aged under 36 years with early diminished ovarian reserve (serum AMH <14 pmol/l and FSH <10 IU/l) were identified in this retrospective study. In 87 of these patients (71.3%) the treating clinician had increased the starting dose of rFSH to 200–300 IU/day because of predicted poor ovarian reserve, while the remaining 35 women (28.7%) were placed on the standard starting dose of 150 IU/day. As this study was a retrospective analysis of IVF outcomes based on individual physicians', clinical practices it had the potential to be open to significant bias. However, as no significant difference in

Table 1 Baseline characteristics in the two study groups

Baseline characteristics	FSH dose adjusted	FSH dose not adjusted	*P*
N	87	35	
Mean age	32.5±0.3	32.2±0.5	NS
BMI	26.6±0.7	26.0±1.3	NS
D3 FSH (IU/L)	7.1±0.3	7.0±0.4	NS
D3 AMH (pmol/L)	9.1±0.3	9.3±0.5	NS
Antral follicle count (2–5.9 mm)	8.4±0.8	8.4±0.9	NS
Aetiology	23 (26%)	16 (46%)	NS
Male			
Female	24 (28%)	10 (29%)	NS
Combined	21 (24%)	5 (14%)	NS
Idiopathic	19 (22%)	4 (11%)	NS

All data expressed as mean±SEM

serum AMH or other markers of ovarian reserve and fertility (maternal age, BMI, early follicular phase FSH, antral follicle count or aetiology of infertility) was observed between the standard and high dose groups (Table 1), significant bias appears unlikely. The two groups appeared to be comparable in terms of predicted response to gonadotrophin stimulation in all respects.

On average both treatment groups produced only seven oocytes per cycle, well below the average 12 oocytes produced by women less than 36 years of age in the author's IVF unit. This observation confirms the clinical utility of serum AMH to predict poor ovarian reserve. Somewhat unexpectedly, upward adjustment of the starting dose of rFSH in predicted poor responders from 150 IU/day to 200–300 IU/day appears to have had no significant effect on any of the important IVF outcomes (Table 2). This upward FSH dose adjustment did not produce any significant improvement in oocytes retrieved (6.82 v 7.0, $p = 0.70$), embryos generated (3.8 v 3.6, $p = 0.59$) or embryo quality in the high versus standard dose groups respectively. Furthermore, there was no difference in the proportion of IVF cycles which were abandoned due to either no response or no embryos available for transfer (15% in the high dose group v 14% standard dose). As increasing the starting dose of rFSH did not result in any significant increase in the number of good quality embryos available for transfer, it is not surprising that dose adjustment failed to produce any significant improvements in pregnancy outcome (Table 3).

No patient experienced OHSS in either study group, thereby suggesting that upward dose adjustment based on an AMH assessment of low ovarian reserve was not a harmful approach. However, this high dose approach did result in the "waste" of an average 1,100 IU of rFSH per cycle (3,108 IU v 2,008 IU, $p=0.001$) for absolutely no improvement in IVF outcomes.

Discussion

Maternal age and basal FSH levels are relatively imprecise measures of ovarian reserve outside the very extremes of reproductive potential (age >40 years, FSH >10 IU/l). Therefore the use of age and FSH to determine starting dose of gonadotrophins in young women, is unlikely to be effective. Previous studies have shown that the addition of other ovarian reserve indices such as ovary volume, doppler and antral follicle count can produce a better COH outcome during IVF treatment than the use of age and basal FSH alone [5]. However, even with this more individualized approach, 23% of patients still did not produce the ideal outcome of 5–14 oocytes. It was therefore hoped that because AMH is the most sensitive marker of ovarian reserve, it may more accurately determine the ideal starting dose of rFSH.

AMH measurements have several theoretical advantages over other markers of ovarian reserve. Firstly, serum AMH has been shown to be the most sensitive predictor of ovarian response to COH compared to serum FSH, inhibin B, oestradiol, antral follicle count and ovary volume [8, 9]. Secondly, unlike serum FSH, inhibin B and oestradiol levels, serum AMH levels appear to be relatively stable throughout the menstrual cycle [29–31], making assessment of ovarian reserve possible at any stage of the cycle. Thirdly, serum AMH levels have the greatest reproducibility with the least variation between cycles of any of the serum markers of ovarian reserve [32]. Finally, as serum AMH is quantified by a relatively simple to conduct ELISA, it does not suffer from the problem of large inter-observer variations as seen in ultrasound assessment of ovarian reserve (antral follicle count, ovarian volume and Doppler assessment). As such, it was believed that AMH would have the greatest capacity to facilitate effective individualization of FSH starting dose during IVF.

Table 2 Effect of FSH dose adjustment on IVF outcomes

IVF treatment parameters	FSH dose adjusted	FSH dose not adjusted	*P*
N	87	35	
Mean number of oocytes retrieved	6.82±0.42	7.0±0.6	NS
Total gonadotrophin administered (IU)	3108±92	2008±136	0.001
Mode of fertilization (%)			
ICSI	413/531 (78%)	134/219 (61%)	NS
IVF	118/531 (22%)	85/219 (39%)	NS
Fertilisation rates (%)			
with ICSI	274/413 (66%)	80/134 (60%)	NS
with IVF	57/118 (48%)	48/85 (57%)	NS
Embryo quality (ICSI + IVF): (%)			
good quality (G1 & G2)	176/331 (53%)	77/128 (60%)	NS
poor quality (G3 & G4)	155/331 (47%)	51/128 (40%)	NS
Mean number of embryos generated	3.8±0.3	3.6±0.4	NS
Mean number of embryos frozen	0.9±0.2	1.0±0.3	NS

Table 3 Effect of FSH dose adjustment on pregnancy outcomes

Pregnancy outcome	FSH dose adjusted	FSH dose not adjusted	*P*
Number of cycles commenced	87	35	
Mean number of embryos transferred	1.0	1.0	NS
Mean day of ET	2.8±0.2	2.9±0.3	NS
Number of patients with fresh ET (%)	74/87 (85%)	30/35 (86%)	NS
Positive βHCG / fresh ET (%)	35/74 (47%)	16/30 (53%)	NS
Positive HCG/ cycle commenced (%)	35/74 (47%)	16/35 (46%)	NS
Clinical pregnancy / fresh ET (%)	33/74 (45%)	15/30 (50%)	NS
Clinical pregnancy / cycle commenced (%)	33/87 (38%)	15/35 (43%)	NS

*Clinical pregnancy defined as fetal heart on 8 week ultrasound.

Several previous studies have shown that patients with good ovarian reserve do benefit from an upward adjustment of their starting dose of rFSH from 100 IU/day to 150 IU/day to 200–300 IU/day, generating an extra one to four oocytes per cycle [23–27]. However, the literature regarding the effectiveness of upward dose adjustment in women with poor ovarian reserve has not shown any consistent benefit. A comparison of IVF outcomes in previous poor responders between a starting dose of 225 IU/day versus 450 IU/day reported only a small increase in the number of retrieved oocytes, but no increase in the number of embryos generated [33]. This suggests that while ultra-high doses of FSH may recruit "resistant" follicles, their oocytes are of poor quality and do not result in the generation of good quality embryos. Another study which compared the number of retrieved oocytes and IVF cancellation rates in previous poor responders found absolutely no benefit from increasing the starting dose of FSH above 150 IU/day [4]. Furthermore, predicted poor responders, based on either marginally elevated levels of basal FSH [23] or low antral follicle count [34], were not shown to benefit from an increase in starting dose of FSH. In support of this theory is the recent publication by Pal et al [35] who have described a reduced likelihood of clinical pregnancy and live birth and a trend towards a higher likelihood of miscarriage with the use of high dosages of gonadotrophin.

These observations are consistent with the findings of the current study.

In the absence of a defect in granulosa cell FSH receptors effecting their sensitivity to FSH stimulation, inadequate local vascular networks for the distribution of gonadotrophins or the presence of neutralizing anti-FSH antibodies, it is unlikely that increasing the dose of FSH will result in an improved IVF response [36]. The recruitment of primordial follicles into the antral follicle pool takes several months and is a process largely independent of FSH stimulation [37]. Administration of high dose FSH for 2 weeks during an IVF cycle does not have the capacity to increase the number of preantral follicles available for growth in that cycle, and therefore is unlikely to influence the number of resulting mature follicles. Only those follicles between 2 mm and 5 mm at the commencement of an IVF cycle have the capacity to respond to FSH stimulation. It is probable that once circulating FSH levels exceed the antral follicles "stimulation threshold", further increases in the dose of stimulation are unlikely to result in any improvement in mature follicle development.

We believe that ovarian reserve assessment using AMH measurements still has clinical utility, despite the current study showing that knowledge of low ovarian reserve prior to commencing a first cycle of IVF, with subsequent upward dose adjustment, does not improve IVF outcomes. Firstly, recent studies have suggested that women with high levels of AMH are at considerably increased risk of developing OHSS [15, 18, 38, 39]. A clinician may use this information to reduce the starting dose of FSH in such "high risk" patients, thereby reducing their chances of developing OHSS. Secondly, AMH has been shown to be a useful predictor of IVF cycle cancellation due to an extremely poor response [9, 18, 20]. This is very useful information prior to commencing IVF treatment as it gives patients a reasonable expectation of likely IVF outcome, thereby reducing surprise and anger when a poor outcome is encountered. Similarly, low AMH levels have been shown to have a negative prognostic influence on the chances of pregnancy during an IVF cycle [18, 19] helping set realistic expectations prior to commencing IVF treatment.

None of the clinicians working within our IVF unit have a special interest in seeing patients with diminished ovarian reserve. Therefore it is unlikely that any one clinician would have seen a different group of patients from another affecting the outcome of this study. This is supported by the observations in Table 1 which show that the main IVF prognostic factors (age, BMI, day three FSH, antral follicle count and aetiology of infertility) do not differ between the patients undergoing treatment by the "dose adjustment" doctors and those treated by doctors who practiced "per protocol". Furthermore, serum AMH levels were almost

identical between the two groups, making a significant bias unlikely.

The results of this study clearly indicate that increasing the starting dose of FSH stimulation in potential poor responders based on low AMH values is not an effective approach. No significant improvement in oocyte or embryo yield, or pregnancy rates was observed following such an upward FSH dose adjustment. While increasing the starting dose above the standard of 150 IU/day did not result in any adverse events such as OHSS, it did consume an extra 1,100 IU of rFSH per IVF cycle. Since the cost of gonadotrophins is one of the major expenditures in IVF treatment, this huge increase in drug cost without any significant improvement in clinical outcome is clearly wasteful and can not be advocated.

Acknowledgements Dharmawijaya Lekamge was supported by an International Post-Graduate Research Scholarship (IPRS) and Adelaide University Scholarship. We wish to thank staff at Repromed for friendly assistance.

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