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Pituitary Down-Regulation Using Leuprolide for the Intensive Ovulation Management of Poor Prognosis Patients Having in Vitro Fertilization (IVF)-Related Treatments

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A review of 118 treatment cycles in 115 women under prolonged GnRH analogue (GnRHa; leuprolide) treatment is presented. Patients were selected for treatment primarily on the grounds of poor previous response to stimulation (n = 40), advanced age (>35 years; n = 29), previous premature luteinizing hormone (LH) surge (n = 30), polycystic ovarian disease (PCO; n = 12), and elevated androgens without evidence of PCO (n = 5). An overall pregnancy rate of 28.8% per treatment cycle was attained, compared with a pregnancy rate of 6.2% (6/97, of which none went to term) in the previous completed treatment cycle for the same patients. Ovarian response, as measured by oocytes recovered and maximum estradiol levels observed, was significantly improved in all groups and this was associated with a prolonged follicular phase, significantly more human menopausal gonadotropin (hMG) stimulation and a relatively high incidence of ovarian hyperstimulation, particularly in pregnant patients. Of specific techniques in the GnRHa cycle, GIFT produced a pregnancy rate per treatment of 50% (10/20); IVF-ET, 22% (8/36); PROST, 28% (13/46); and TEST, 19% (3/16). No cycles were abandoned, compared with a cancellation rate of 24% in previous cycles without GnRHa. Patients with PCO performed particularly well on GnRHa management, with a pregnancy rate per treatment of 58% (7/12). Pregnancy rates per treatment for the other groups were as follows: elevated age, 27% (9/33), high androgens, 40% (2/5); premature LH surges, 32% (9/28); and poor responders, 17.5% (7/40). A comparison using patients undertaking IVF-ET cycles in 1987 and 1988 shows that the use of GnRHa treatment in the poor-prognosis groups lifts their performance into line with that seen in the "good"-prognosis groups. We conclude that pituitary down-regulation with GnRHa (long regimen) offers significant advantages for ovarian management in most groups of infertility patients and it is now being evaluated for routine use in the majority of cases in our practice.

KEY WORDS: Lucrin; ovulation induction; assisted conception; pregnancy; in vitro fertilization.

INTRODUCTION

It is now recognized that the use of GnRH analogues (GnRHa) in combination with gonadotropin stimulation may be beneficial in superovulatory regimens, particularly for patients with ovulatory disorders such as polycystic ovary syndrome (PCO), elevated baseline gonadotropins, premature LH (luteinizing hormone) surge, and premature luteinization (1–16). Pituitary suppression is more effective when therapy commences in the midluteal rather than the early follicular phase (17), and there is evidence that the use of GnRHa in the follicular phase ("flare-up" technique) may in fact be detrimental to oocyte maturation (18) and, while increasing the numbers of oocytes recovered, may not increase the total number of embryos developing (19). In addition to its use in poor-prognosis patients, GnRHa therapy is now starting to be seen as the preferred routine stimulation approach by several groups (20) including our own.

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We report here on a series of 118 treatment cycles in patients recognized as either responding poorly in previous treatment cycles or otherwise being of poor prognosis for normal ovarian management. As it was not possible in retrospect to establish an ideal control group for these patients we have included, for additional comparison in the analysis, data from our in vitro fertilization and embryo transfer (IVF-ET) program for two additional groups: (i) all patients for 1987—including those of poor prognosis, treated using a combination of clomiphene citrate and human menopausal gonadotropin (CC-hMG); and (ii) all non-Lucrin-treated "good"-prognosis IVF-ET patients for 1988 on CC-hMG stimulation. This provides additional insight to changing modes of treatment during a period when our program was experiencing increasing success rates (21).

MATERIALS AND METHODS

Patient Categorization and Treatment

Four treatment options are included: IVF-ET, gamete intrafallopian transfer (GIFT), pronuclear-stage tubal transfer (PROST), and tubal embryo stage transfer (TEST). Indications for including patients in treatment programs at PIVET Medical Centre were, briefly, as follows (21).

IVF-ET. Indicated for all cases of tubal infertility.

GIFT. Indications for GIFT treatment were idiopathic infertility, negative sperm/mucus interaction, failed donor insemination/AIH, endometriosis, moderately severe oligozoospermia (<5 million motile sperm/ml of semen), and the presence of antisperm antibodies in the male only with no significant asthenozoospermia. Cases of previous tubal reconstructive surgery with no subsequent pregnancy but with evidence of at least one patent fallopian tube were initially treated by GIFT but are no longer included for any tubal transfer procedure, as ectopic pregnancy rates are high (21).

PROST. PROST treatment was indicated for patients with male-factor infertility, antisperm antibodies in the female, repeated GIFT failures, or conversion from GIFT if the egg number is low or the sperm quality questionable for fertilization. PROST is also used in cases of synchronous ovum donation.

TEST. Indications for TEST treatment were severe male-factor infertility with a possible need for reinsemination of oocytes, evaluation after pentoxifylline treatment (22) or micromanipulation in vitro, and uncertain tubal access (no longer included due to risk of ectopic pregnancy) (21). TEST is also used for frozen embryo transfer and cases of asynchronous oocyte donation.

A total of 115 patients in 118 consecutive treatment cycles has been considered. They were grouped according to their main indication as follows:

(1) poor responders in previous treatment cycles (n = 40);
(2) advanced age (>35 years, no other endocrinological indication; n = 33);
(3) premature LH surge in the previous cycle (less than 6 consecutive days of sustained E_2 rise; n = 28);
(4) PCO cases—raised LH/FSH (follicle-stimulating hormone) ratio and /or multifollicular ovaries visualized by ultrasound on Day 2 (n = 12); and
(5) elevated androgens without PCO (n = 5).

It was not possible to compare the patients with matched controls, so the results of the GnRHa treatment cycle were compared with the immediate previous cycle. Previous treatment options included donor insemination (DI), artificial insemination by partner's spermatozoa (AIH), and timed intercourse (IC). Assessment cycles were included in the analysis, as for many cases these were the only available; however, these were not included in calculation of results of treatment. For comparison, additional information is also presented on patients undergoing IVF-ET in 1987 and 1988 on CC-hMG stimulation. The 1987 group included those judged of poor prognosis, while for the 1988 group this category of patient was moved into Lucrin therapy.

Stimulation Regimen

Leuprolide injections (1 mg/day; Abbott, Australasia; dosage according to manufacturer's recommendation) commenced on Day 21 of the previous menstrual cycle and graded hMG (Serono, Rome) stimulation commenced when serum estradiol levels were less than 200 pM, usually on Day 2 of the treatment cycle. The cycle was monitored by daily assay of serum progesterone (P), luteinizing hormone (LH), and estradiol 17-β (E_2) and by follicular ultrasonography as described in detail elsewhere (23,24). Initial levels of hMG stimulation were

Table I. Previous and Present Treatment Cycles

Previous cycle	Treatment this cycle				
	GIFT	IVF-ET	TEST	PROST	Total
GIFT	8	0	1	6	15
IVF-ET	1	19	1	1	22
PROST/TEST	0	2	13	29	44
DI/AIH/IC	6	1	0	4	11
Observation cycle	4	10	1	6	21
Repeat GnRHa cycle	1	4	0	0	5
Total	20	36	16	46	118

graded according to response up to a maximum of 11 ampoules/day. Leuprolide administration ceased on the day of giving a triggering injection of 10,000 IU human chorionic gonadotropin (hCG) (Profasi; Serono, Rome). This was timed primarily on the basis of 7 days' consecutive rise of E_2 over baseline. Follicle size was monitored by ultrasound but was not relied on as the major index of follicular activity. Determination of clinical pregnancy rates and other outcomes were as described elsewhere (24).

RESULTS

Comparison with Previous Cycles

Details of previous cycle treatments and outcomes are given in Tables I and II. The overall pregnancy rate per treatment, discounting 16 previous observation and 5 repeat GnRHa cycles, was 6.2% (6/97) and none of these pregnancies went to term (4 blighted ova, 1 spontaneous abortion, and 1 ectopic

Table II. Previous Treatment Cycle: Outcomes and Etiology

Treatment group in GnRHa cycle	Etiology					
	PR	AGE	PS	Androgens	PCO	Total
GIFT						
Pregnant	3 SBE[a]	2 BB	0	0	0	5
Not pregnant	0	1	3	0	2	7
Canceled	1	0	2	0	2	5
Tracking	1	0	0	0	1	2
Repeat	1 1	0	0	0	0	1
IVF-ET						
Pregnant	0	0	0	0	0	0
Not pregnant	8	6	5	0	0	19
Canceled	0	0	3	0	0	3
Tracking	2	7	0	1	0	10
Repeat	1	1	1	1	0	4
PROST						
Pregnant	0	0	0	0	0	0
Not pregnant	12	7	8	1	1	29
Canceled	4	2	5	1	1	13
Tracking	0	1	0	0	3	4
TEST						
Pregnant	1 B	0	0	0	0	1
Not pregnant	4	5	1	2	0	12
Canceled	1	1	0	0	1	3
Tracking	0	0	0	0	0	0
Total						
Pregnant	4	2	0	0	0	6
Not pregnant	25	19	17	3	3	67
Canceled	6	3	10	1	4	24
Tracking	3	8	0	0	5	16
Repeat	2	1	1	1	0	5
	40	33	28	5	12	118

[a] Pregnancy outcomes: B, blighted ovum; S, spontaneous abortion; E, ectopic pregnancy.

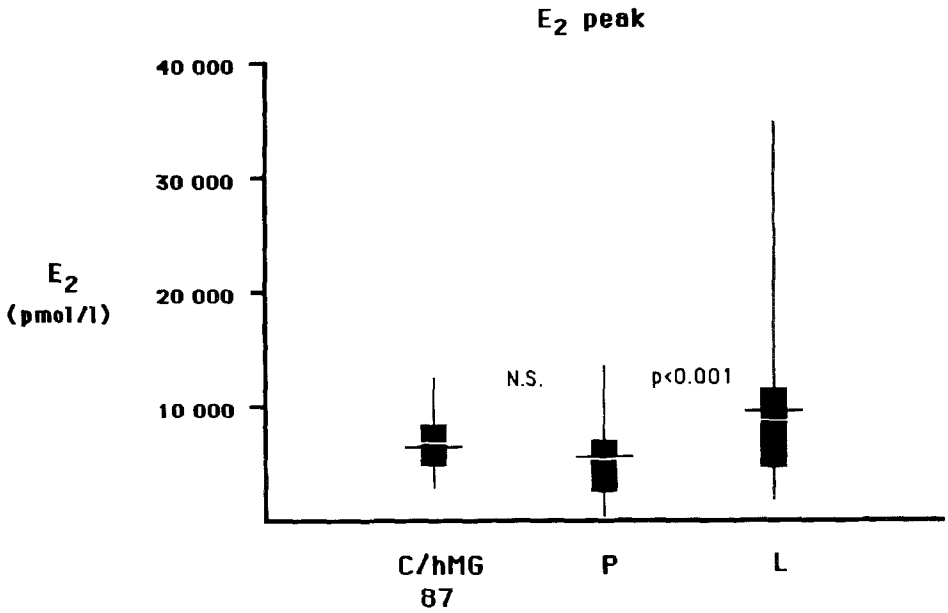

Fig. 1. Maximum estradiol levels attained in previous treatment cycles (P) and in leuprolide-managed cycles (L). The nonnormally distributed data are presented as Tukey box-and-whisker plots indicating maximum range (vertical line), arithmetic mean (cross-line), and 25, 50, and 75% quartiles (box components). The levels are significantly different ($P < 0.001$ by Mann–Whitney and Wilcoxon tests).

pregnancy). Twenty-one of the cycles (17.8%) were canceled before reaching the point of treatment, due mostly to poor ovarian response or premature LH surges. In a further 13 cycles there was failed fertilization in an IVF, PROST, or TEST attempt; 6 of these could be attributed to seminal defects, but the remainder were apparently associated with poor oocyte quality due to poor ovarian response.

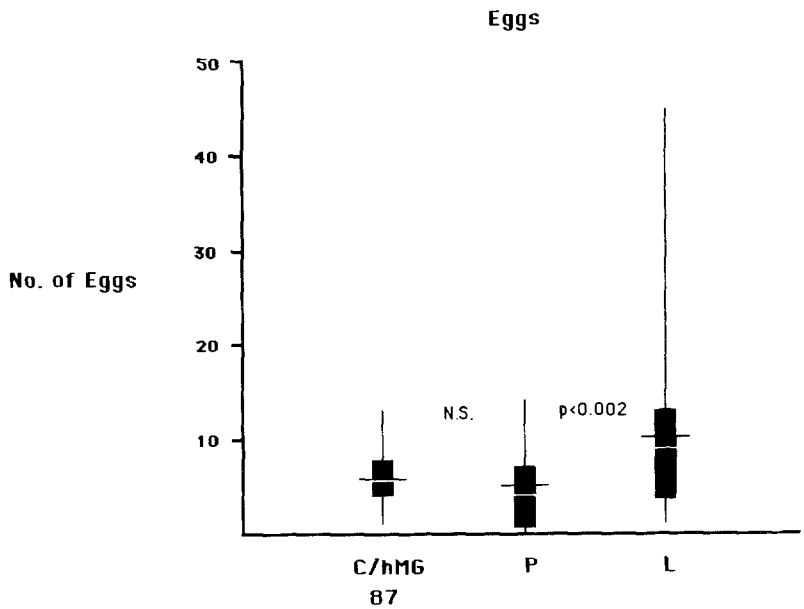

Fig. 2. Number of eggs recovered per treatment cycle ($P < 0.002$).

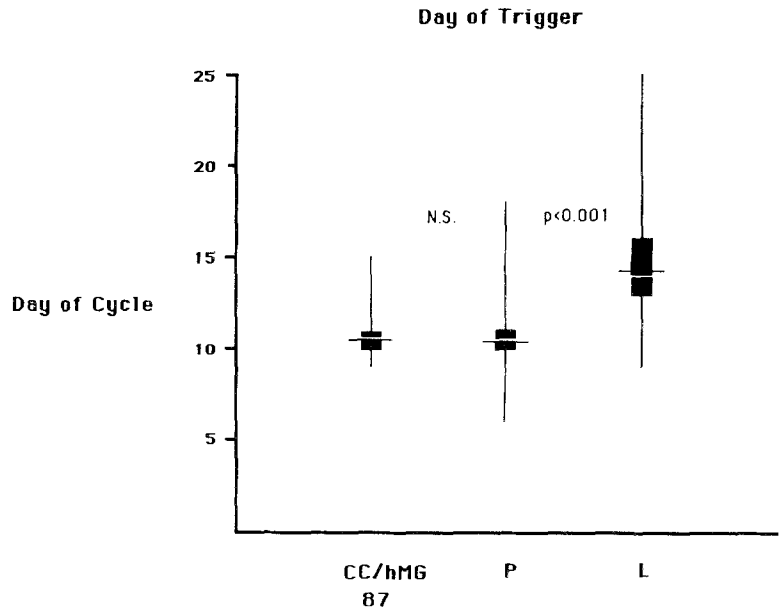

Fig. 3. Day of administering hCG ovulation trigger ($P < 0.001$).

Comparison of the Treatment Cycle with the Previous Cycle

Ovarian performance under GnRHa treatment as compared with the previous cycle and with CC-hMG IVF-ET data for 1987 and 1988 is presented in Figs. 1–4 and Table VI. As the data were not normally distributed for the most part, they have been displayed as Tukey box-and-whisker plots indicating the range, 25, 50, and 75% quartiles, and arithmetic mean.

In the treatment cycle a mean of 10.13 oocytes was recovered, compared with 5.18 (0–14) for relevant previous cycles ($P < 0.001$, Mann–Whitney and Wilcoxon nonparametric tests). The mean day of administering hCG trigger was advanced from a mean previous day 10.9 of the cycle to 14.2 in the GnRHa cycle ($P < 0.001$). A mean total of 68.1

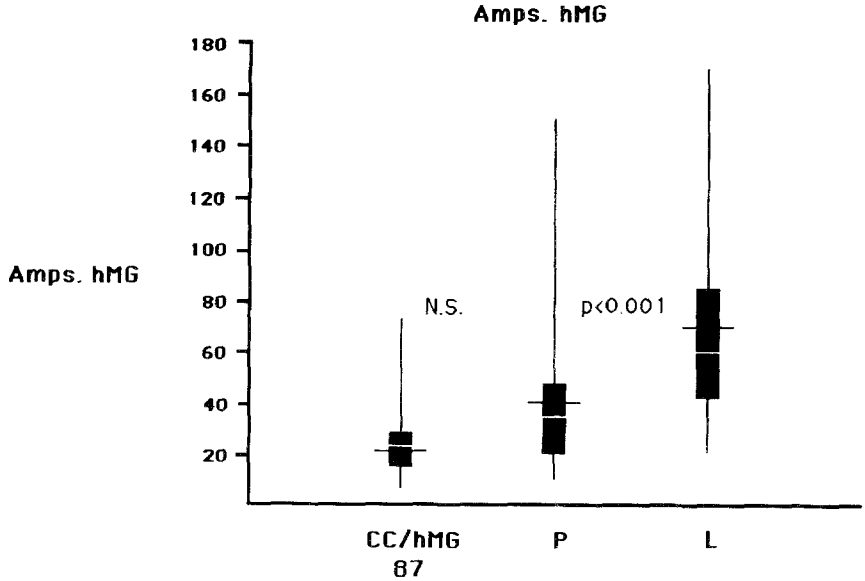

Fig. 4. Ampoules of hMG administered ($P < 0.001$).

Table III. Lucrin Treatment Cycle: Pregnancies/Treatment

Treatment	Primary indication					Total
	PR	AGE	PS	Androgens	PCO	
GIFT	4/7	1/3	2/5	0/0	3/5	10/20 (50.0%)
IVF-ET	1/11	4/14	2/9	0/1	1/1	8/36 (22.2%)
PROST	1/16	3/10	5/13	1/2	3/5	13/46 (28.3%)
TEST	1/6	1/6	0/1	1/2	0/1	3/16 (18.7%)
Total	7/40 (17.5%)	9/33 (27.3%)	9/28 (32.1%)	2/5 (40.0%)	7/12 (58.3%)	34/118 (28.8%)

ampoules of hMG was administered in the GnRHa cycle, compared with 41.2 ($P < 0.001$), and peak E_2 figures improved from a mean of 5398 to 9430, p*M* ($P < 0.001$).

Table III shows the outcome in the GnRHa treatment cycle. The overall pregnancy rate was 28.8% per treatment or 33.0% per oocyte/embryo transfer. This compares favorably with the pregnancy rate of 6.2% in previous treatment cycles as discussed above.

In 18 cycles ovarian hyperstimulation was manifested by abdominal distension and discomfort. In five of these cases the symptoms were severe enough to warrant abdominal paracentesis and drainage (overall incidence of severe hyperstimulation, 4%). This syndrome was usually associated with pregnancy. Thus, mild to severe hyperstimulation was observed in 14 of the 34 pregnancy cycles (41%) but in only 4 of the 84 nonpregnancy cycles (4.7%). In hyperstimulated patients high peak serum E_2 levels were also seen, with a mean of 13596 p*M*, compared with 8465 p*M* in the others ($P < 0.001$ by *t* test). Thus while the ovarian response as measured by estradiol levels would appear to have predisposed toward hyperstimulation in this group of poor-prognosis patients, another important etiological factor for this syndrome was pregnancy itself.

Comparison with 1987 and 1988 CC-hMG IVF-ET Patients

These results are presented in Table IV. Fertilization rates for the poor prognosis patients on Lucrin (IVF-ET only) were significantly better than those seen for both the 1987 IVF-ET group ($P < 0.001$ by chi-square analysis) and the 1988 group. The pregnancy rate per treatment cycle was similar in both the Lucrin-treated poor-prognosis group and the 1988 IVF-ET patients, whereas that for the 1987 group (including poor-prognosis patients) was significantly poorer than the rates for both the Lucrin group ($P < 0.001$) and the 1988 "good"-prognosis group ($P < 0.05$).

Table IV. Fertilization Rate and Pregnancy Rate for Lucrin vs 1987 and 1988 CC/hMG Groups

	Fertilization rate	Pregnancy rate
Lucrin, 1988	430/592 (73%)[a,*]	34/118 (28.8%)[x]
CC/hMG, 1987	284/488 (58%)[b]	7/82 (8.5%)[y]
CC/hMG, 1988	132/203 (65%)[b]	7/27 (26%)[x]

* Groups with different suffixes are significantly different from each other by chi-square analysis.

Results for embryo quality are presented in Table V. Embryos were graded subjectively in ascending quality from 1 to 4, considering factors such as blastomere regularity and clarity, degree of fragmentation, and cleavage stage. It has been established that such grading systems by experienced embryologists are good predictors of successful pregnancy (25). Contingency table analysis revealed significant differences between all groups in the distribution of embryos between different grades (chi 21.5, 6 df, $P < 0.001$). A pairwise comparison between groups showed that this was due mainly to the 1987 figures ($P < 0.001$ compared with Lucrin 1988 and $P < 0.05$ compared with CC-hMG 1988), and examination of the data reveals more poor-quality (Grade 1) embryos and fewer top-quality (Grade 4) embryos in this group. No significant differences between the Lucrin 1988 and the CC-hMG 1988 groups could be detected.

DISCUSSION

When comparing the previous cycle with the Lucrin cycle in these poor-prognosis patients, it is

Table V. Distribution of Embryo Quality Ratings

Group	Embryo quality rating				Total
	1	2	3	4	
Lucrin, 1988	2%	34%	54%	10%	258
CC-hMG, 1987	10%	30%	55%	5%	284
CC-hMG, 1988	4%	30%	53%	13%	121

Table VI. Summary of Data for Number of Eggs Recovered, Day of hCG Trigger, Number of Ampoules of hMG Administered, and Peak E_2 Levels Achieved

	Lucrin			Previous		
	Mean	Median	Range	Mean	Median	Range
Eggs	10.1	9.0	1–44	5.2	4.0	0–14
Day of trigger	14.2	14.0	9–25	10.9	11.0	6–18
Ampoules hMG	68.1	60.0	21–189	41.2	36.0	10–152
Peak E_2	9430	8570	1,860–34,250	5398	5420	29–13,200[a]

[a] Low E_2 "peak" refers to stage of cancellation.

clear that the ovarian response under GnRHa management resulted in a significant prolongation of the follicular phase, greater oocyte recovery rates, and higher maximum E_2 responses, all in response to higher dose rates of gonadotropin. Efficiency of response can be expressed in terms of the units of peak E_2 observed per the number of oocytes recovered: this declined from a mean of 1545 p*M* in the previous cycle (range, 496–5890) to 1130 p*M* (278–3421) in the GnRHa cycle ($P < 0.0028$, Mann–Whitney; $P < 0.0194$, Wilcoxon test). These observations thus confirm those from other groups concerning the efficacy of long-term GnRHa down-regulation in the management of poor-prognosis patients. It could be argued that the previous treatment cycle is a poor control for assessing ovarian response and that a randomized trial would be more appropriate. However, the analytical approach here has been used by other groups (12,15) and the emerging perspective is that the clear therapeutic benefits offered by GnRHa management make such clinical trials inappropriate or even unethical in not offering such poor-prognosis patients the best possible treatment. With this deficiency in experimental design in mind, IVF-ET patients subjected to CC-hMG stimulation in 1987 and 1988 were included here as additional comparison groups, as their responses to ovarian stimulation were generally representative of the infertile population being seen by our clinic and also because detailed information on fertilization rates and ensuing embryo quality is available, these being relatively objective measures of response to stimulation regimens. It is apparent from both the fertilization rates and the pregnancy rates that in 1987, when poor-prognosis patients were not selected for special treatment, overall results were poor. In contrast, the use of GnRHa therapy in 1988 brought both parameters into line with those seen in the "good"-prognosis patients. It must be appreciated, however, that the groups are not strictly comparable. Patients on leuprolide received hMG alone, while the other groups received CC-hMG. This difference in stimulation regimen introduces a second major variable, so some of the improvement in results might relate to the changed stimulation (e.g., absence of CC) rather than to leuprolide alone.

It is not yet clear whether the better results for poor-prognosis patients seen with long-term GnRHa therapy are due to qualitative changes in oocytes and embryos or to quantitative factors such as the ability to select "better" oocytes and embryos from those recovered. An additional major factor may be improved uterine receptivity following a more prolonged follicular phase, as suggested by Testart *et al.* (26).

We conclude that pituitary down-regulation using the long regimen of leuprolide coupled with stimulation with hMG alone significantly improves the chance of pregnancy for a range of patients having IVF-related procedures but who may be categorized as poor-prognosis cases. Furthermore, the benefits of the leuprolide/hMG regimen in reducing the chance of cancellation of treatment cycles and avoiding LH surges, thereby enabling a totally programmed organizational schedule, means that the regimen should be considered for all cases being treated in the program, and this is now standard for the majority of patients at PIVET. However, we still see patients who are highly resistant to gonadotropin stimulation despite leuprolide down-regulation. Future options for such women might include the use of growth hormone in combination with gonadotropin stimulation (27).

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