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Comparison of Exogenous Gonadotropins and Pulsatile Gonadotropin-Releasing Hormone for Induction of Ovulation in Hypogonadotropic Amenorrhea*

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ABSTRACT

To compare the efficacy and safety of ovulation induction with exogenous gonadotropins *vs.* pulsatile GnRH in patients with hypogonadotropic amenorrhea, results from 30 patients in 111 cycles of gonadotropins and 41 patients in 118 cycles of pulsatile GnRH were analyzed retrospectively. Exogenous gonadotropins were administered using an individually adjusted protocol, using a starting dose of 150 IU. Pulsatile GnRH was delivered iv at a physiological frequency based upon our normative data. The doses administered ranged from 75–250 ng/kg. Preovulatory serum estradiol (E_2) and luteal phase progesterone (P) levels were compared to those in normal cycling women (n = 87).

The mean body mass index, age, and baseline gonadotropin levels were similar in the two groups. Overall ovulatory rates and conception rates per cycle and per patient were not significantly different between the two groups. However, the cumulative chance of conception after six cycles of treatment by life table analysis appeared to be higher with pulsatile GnRH treatment (96%) than with exogenous gonadotropins (72%). The risk of multiple gestation was also higher with exogenous gonadotropins (14.8% *vs.* 8.3%), although this was not statistically significant. All higher order multiple gestations (triplets or more) occurred in the gonadotropin-treated group. More than two dominant follicles were seen on ultrasound in 47.6% of gonadotropin-treated cycles compared to 18.9% of cycles with pulsatile GnRH treatment ($P < 0.01$). Three or more follicles were seen in 16.6% of the gonadotropin cycles compared to 5.4% with pulsatile GnRH ($P < 0.05$). No case of severe ovarian hyperstimulation was observed in either group, although the mean luteal phase ovarian size was significantly higher in the gonadotropin group ($P < 0.05$). Mean peak preovulatory E_2 levels were significantly higher in the gonadotropin group (1684.5 ± 124.4 *vs.* 1315.3 ± 74.9 pmol/L; $P < 0.05$). The mean luteal phase P level 1 week after ovulation was significantly higher than normal in the gonadotropin group (84.9 ± 10.8 *vs.* 61.1 ± 3.2 nmol/L; $P < 0.05$), but was not significantly different from that in the pulsatile GnRH group (70.3 ± 6.0 nmol/L).

We conclude that pulsatile GnRH, when compared to exogenous gonadotropins, results in high rates of ovulation and conception, but a decreased risk of multiple folliculogenesis, higher order multiple gestations, and ovarian enlargement. In addition, more physiological preovulatory E_2 levels and luteal phase P levels are observed with pulsatile GnRH compared to exogenous gonadotropin treatment. Therefore, pulsatile GnRH would appear to be the treatment of choice for ovulation induction in hypogonadotropic amenorrhea. A prospective randomized trial of exogenous gonadotropins *vs.* pulsatile GnRH is necessary to further clarify this important issue. (*J Clin Endocrinol Metab* **77:** 125–129, 1993)

HYPOTHALAMIC or hypogonadotropic amenorrhea is a disorder of ovulation, characterized by a spectrum of abnormal patterns of endogenous hypothalamic GnRH secretion, all of which are insufficient to sustain normal folliculogenesis and subsequent ovulation (1–4). Therefore, these GnRH-deficient patients are ideal candidates for exogenous GnRH replacement.

Until recently, only two agents were available for ovulation induction in this population. Clomiphene citrate, whose mechanism of action is to increase FSH through blockade of estrogen negative feedback, is often ineffective in this hypoestrogenic group. Exogenous gonadotropins act directly on the ovary to stimulate folliculogenesis, resulting in high rates of ovulation and conception. However, gonadotropin therapy is associated with a significant risk of complications, including multiple gestation, which is estimated to be as high as 24–50% for hypogonadotropic patients (5–7), and ovarian hyperstimulation syndrome, a potentially life-threatening complication (8).

There are several theoretical advantages to pulsatile GnRH compared to gonadotropin therapy. Exogenous pulsatile GnRH maintains normal pituitary-ovarian feedback mechanisms, employing rising levels of estradiol (E_2) to restrain endogenous FSH secretion, resulting in the development of a single follicle (9). With the potential decreased risk of multiple folliculogenesis, multiple gestation, and ovarian hyperstimulation, a decreased need for intensive monitoring and possibly a decrease in cost would be anticipated. To date, there have been no direct comparisons of these two forms of therapy using uniform diagnostic criteria and monitoring tools, and identified outcome measures to compare results. To explore issues of efficacy and safety with exogenous gonadotropins and pulsatile GnRH, we have completed a retrospective analysis of patients with hypogonadotropic amenorrhea undergoing ovulation induction with a standard regimen of exogenous gonadotropins or pulsatile GnRH.

Subjects and Methods

Subjects

Forty-one patients with hypogonadotropic amenorrhea underwent 118 cycles of pulsatile GnRH, with 30 patients receiving exogenous

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gonadotropins for 111 cycles. Hypogonadotropic amenorrhea was characterized by the absence of menses for at least 6 months and low to normal gonadotropin levels compared to those in our normal population (n = 87). In addition, patients were of normal body weight (between 10th and 90th percentile of weight for height by the Sargent scale), had no history of excessive exercise, and had no evidence of androgen excess (no hirsutism or acne, and normal serum androgen levels when available). In addition, patients had normal TSH and PRL levels. Although the majority of patients had no evidence of a central nervous system defect, 11 patients in the exogenous gonadotropin group had hypogonadotropic amenorrhea due to neuroanatomical causes, including previous surgery or cranial irradiation for a history of pituitary or suprasellar tumors. Hysterosalpingograms were obtained before treatment in both groups to verify tubal patency. Postcoital tests and/or semen analyses were performed routinely, with normal parameters considered to be a sperm concentration greater than 20 million/mL with greater than 50% motility. Patients considered to have male factor infertility were not included in this study, with the exception of one couple in the exogenous gonadotropin group undergoing artificial insemination with donor sperm.

Normal subjects (n = 87) had daily blood samples taken across a menstrual cycle, as previously described (10). The women were euthyroid, normoprolactinemic, of normal body weight, and taking no medication. All had menstrual cycle lengths between 25–35 days and had evidence of ovulation in the previous cycle [midluteal phase progesterone (P) level >19 nmol/L and/or a biphasic body temperature chart].

Protocol

Exogenous gonadotropin regimen. Exogenous gonadotropins were administered im daily according to the protocol of Brown *et al.* (11), using a starting dose of 150 IU. If there was evidence of follicular development by plasma E_2 and ultrasound determinations on day 5 of treatment, the same dose was continued until follicular diameter was greater than or equal to 1.8 cm, with a corresponding E_2 level of approximately 734 pmol/L·follicle. If there was no evidence of follicular development, the dose was increased by approximately 30%. An ovulatory dose of hCG (3000–5000 U, im) was given at the time of follicular maturation, but was withheld (cycle cancelled), if E_2 was greater than 4405 pmol/L or if there were more than three dominant follicles, as determined by ultrasound. Luteal phase ultrasound was performed 7 days after the ovulatory dose of hCG to determine whether hyperstimulation was present, and small supplemental doses of im hCG (500, 1500, and 500 U) were given for luteal phase support 7, 10, and 13 days, respectively, after ovulatory hCG administration. However, if the midluteal ovarian diameter was greater than 6–7 cm, vaginal P suppository supplements (25 mg twice daily) were administered instead of hCG.

Pulsatile GnRH regimen. Pulsatile GnRH was administered iv for all GnRH treatment cycles. Only cycles employing doses of 75–250 ng/kg were analyzed, as we have previously shown that a dose of 75 ng/kg is required to mimic the normal physiology of an ovulatory cycle most closely (9), while 25 ng/kg is a subphysiological dose (12). The frequency of delivery was variable across the cycle, as previously described (9, 12), based on the endogenous hypothalamic GnRH pulse frequencies in normal women (10). Studies using pulsatile GnRH were approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, and signed informed consent was obtained from each subject.

Clinical monitoring. Clinical monitoring included serial pelvic ultrasounds (including one luteal phase ultrasound), performed using a 5-mHz transvaginal convex array probe or a 3.5- to 5-Hz transabdominal probe. Serum E_2 levels were monitored daily until ovulation in the gonadotropin group, and serum P levels were determined 7, 10, and 13 days after the ovulatory dose of hCG. P levels on day 7 were drawn before the administration of hCG or P supplements. In the pulsatile GnRH group, midcycle urinary LH monitoring was performed, and daily blood samples for E_2 and P were assayed at the completion of each treatment cycle.

Assays

Plasma LH, FSH, E_2, and P concentrations were measured by RIA, as previously described (13, 14). All samples from an individual cycle were measured in the same assay, with the exception of plasma E_2 levels in exogenous gonadotropin cycles, which were assayed daily using an extracted E_2 assay (13).

Data analysis

Treatment cycles were considered ovulatory if a luteal phase serum P level was greater than 19 nmol/L (on day 7 after the ovulatory dose of hCG for the gonadotropin group). Pregnancies were defined by a positive serum hCGβ. For exogenous gonadotropin cycles, hCGβ levels were determined at least 5 days after the last luteal phase hCG supplement. Rates of ovulation, conception, multiple gestation, and spontaneous abortion were compared using χ^2 analysis. In addition, preovulatory follicle number and cycle cancellation rate were compared using χ^2 analysis. *t* Tests were used to compare ovarian size 7 days after the ovulatory dose of hCG in the exogenous gonadotropin group and 7 days after the urinary LH surge in the pulsatile GnRH group. Only transvaginal measurements were used for calculation of mean ovarian size (exogenous gonadotropin group, n = 7; GnRH group, n = 12). In addition, *t* tests were used to compare patient baseline characteristics, peak preovulatory serum E_2, and serum P levels drawn 7 days after ovulation. E_2 and P levels were also compared to our database of normally cycling women (n = 87).

Results

Baseline parameters

Baseline clinical and biochemical characteristics showed no significant differences between the pulsatile GnRH and gonadotropin patients in terms of age, body mass index, LH, FSH, or E_2 (Table 1). Semen analyses were reported as normal, with the exception of one couple in the exogenous gonadotropin group undergoing artificial insemination with donor sperm.

Ovulatory and conception rates

Ovulatory rates (percentage of cycles resulting in ovulation) and conception rates (percentage of conceptions per treatment cycle) are shown in Table 2. The overall ovulatory

TABLE 1. Baseline clinical and biochemical characteristics

	Pulsatile GnRH	hMG
Age (yr)	31.4 ± 0.9	29.9 ± 0.9
BMI	24.3 ± 0.9	24.5 ± 1.4
LH (IU/L)	4.7 ± 0.8	6.1 ± 1.0
FSH (IU/L)	6.5 ± 0.8	7.1 ± 0.8
E_2 (pmol/L)	121.9 ± 5.9	112.7 ± 10.3

hMG, Human menopausal gonadotropin; BMI, body mass index.

TABLE 2. Clinical outcomes of pulsatile GnRH *vs.* exogenous gonadotropins in hypogonadotropic amenorrhea

	Pulsatile GnRH (75–250 ng/kg)	hMG
Ovulatory rates (%)	93	97
Conception rates (%)		
% of cycles	29	25
% of patients	73.9	60
Spontaneous abortion rate (%)	23.8	16.6

hMG, Human menopausal gonadotropin.

rate in the exogenous gonadotropin group was 97% compared to 93% in the pulsatile GnRH group (P = NS). Pulsatile GnRH conception rates per treatment cycle (29%) or per patient (73.9%) were not significantly different from those in the patients treated with exogenous gonadotropins (25% and 60%, respectively). Although the rate of spontaneous abortion was higher in the pulsatile GnRH group (23.8% *vs.* 16.6%), this was not a significant difference. The percentage of viable term pregnancies with exogenous gonadotropin treatment was 21%, similar to the 23% with pulsatile GnRH (P = NS). Life table analysis of conceptions corrects for patients who conceive or discontinue therapy (Fig. 1). This analysis demonstrates that the cumulative chance of conceiving after six treatment cycles of pulsatile GnRH (96%) was higher than that after treatment with exogenous gonadotropins (72%). The cumulative chance of conceiving plateaued after the fourth cycle of gonadotropin therapy, whereas that for pulsatile GnRH continued to increase through the sixth cycle.

Multiple gestations

The risk of multiple gestation, while higher in the gonadotropin group (14.8%) than with pulsatile GnRH (8.3%), was not significantly different (Table 3). All multiple gestations with pulsatile GnRH were twin pregnancies, with no higher order multiples. In contrast, 75% of multiple gestations in the exogenous gonadotropin group were higher order pregnancies (triplets or more). More than two dominant follicles were seen on ultrasound in 47.6% of exogenous gonadotropin cycles, significantly higher than the 18.9% seen with pulsatile GnRH ($P < 0.01$). In addition, 16.6% of exogenous gonadotropin cycles resulted in more than three dominant follicles, significantly higher than the 5.4% seen with pulsatile GnRH ($P < 0.05$).

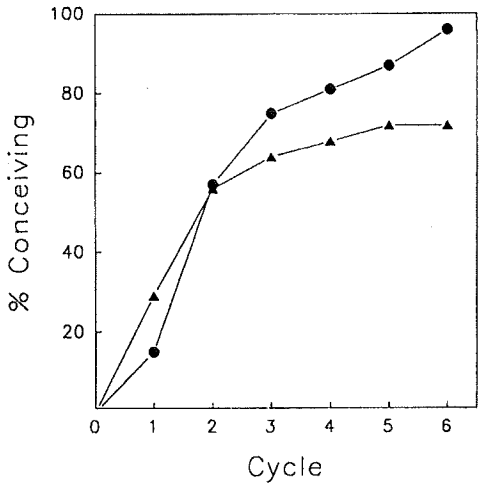

FIG. 1. Life table analysis correcting for patients who conceived or discontinued therapy. The cumulative chance of conceiving after six treatment cycles of pulsatile GnRH (●) is 96% *vs.* 72% for exogenous gonadotropin treatment (▲).

TABLE 3. Multiple gestations with pulsatile GnRH *vs.* exogenous gonadotropins in hypogonadotropic amenorrhea

	Pulsatile GnRH (75–250 ng/kg)	hMG
Multiple gestations (%)	8.3	14.8
Follicle no.		
%> 2 follicles	18.9	47.6[a]
%> 3 follicles	5.4	16.6[b]

hMG, Human menopausal gonadotropin.
[a] $P < 0.01$.
[b] $P < 0.05$.

Midluteal ovarian size

There were no cases of severe ovarian hyperstimulation syndrome in either group using the criteria of Rabau *et al.* (15). However, the mean maximum ovarian diameter on luteal phase ultrasound 7 days after the ovulatory dose of hCG (gonadotropin group) or the LH surge (GnRH group) was significantly greater in the gonadotropin group than in the pulsatile GnRH group (6.2 × 5.5 *vs.* 3.3 × 2.8 cm; $P < 0.05$). The cycle cancellation rate for the exogenous gonadotropin group due to multiple follicular development and/or high serum E_2 levels was 4.5%, whereas no pulsatile GnRH cycles required cancellation ($P < 0.05$).

Biochemical evidence of hyperstimulation

The mean peak preovulatory E_2 level (Fig. 2) for the exogenous gonadotropin group was 1684.5 ± 124.4 pmol/L, significantly higher than that in normal women (1086.6 ± 38.5 pmol/L; $P < 0.01$) or in women treated with any dose of GnRH (1315.3 ± 75.9 pmol/L; $P < 0.05$) or GnRH 75 ng/kg (1230.8 ± 98.0 pmol/L; $P < 0.05$). The mean P level 7 days after ovulatory hCG treatment in the exogenous gonadotropin group was 84.9 ± 10.8 nmol/L, significantly higher than that in the normal women (61.1 ± 3.2 nmol/L; $P < 0.05$). The mean P level for all GnRH doses (70.3 ± 6.0 nmol/L) and GnRH treatment [75 ng/kg (70.9 ± 6.9 nmol/L)] was lower than that in the gonadotropin group, although this did not reach statistical significance.

Discussion

This study represents the first direct comparison of the efficacy and safety of exogenous gonadotropins *vs.* pulsatile GnRH for patients with hypogonadotropic amenorrhea. Due to the hypoestrogenic status of these patients, ovulation induction with the estrogen antagonist clomiphene citrate is often ineffective. Therefore, in the majority of hypogonadotropic patients, successful induction of ovulation has required the use of exogenous gonadotropins. However, this study demonstrates that the ovulatory and conception rates of pulsatile GnRH, a newer ovulation induction agent, are comparable to those achieved with exogenous gonadotropins. In this retrospective analysis, there were no significant differences in the baseline characteristics of patients receiving pulsatile GnRH or exogenous gonadotropins. The ovulatory rates for hypogonadotropic patients receiving exogenous gonadotropins in this study are high (97%), and the conception rates per cycle (25%) and per patient (60%) are similar to

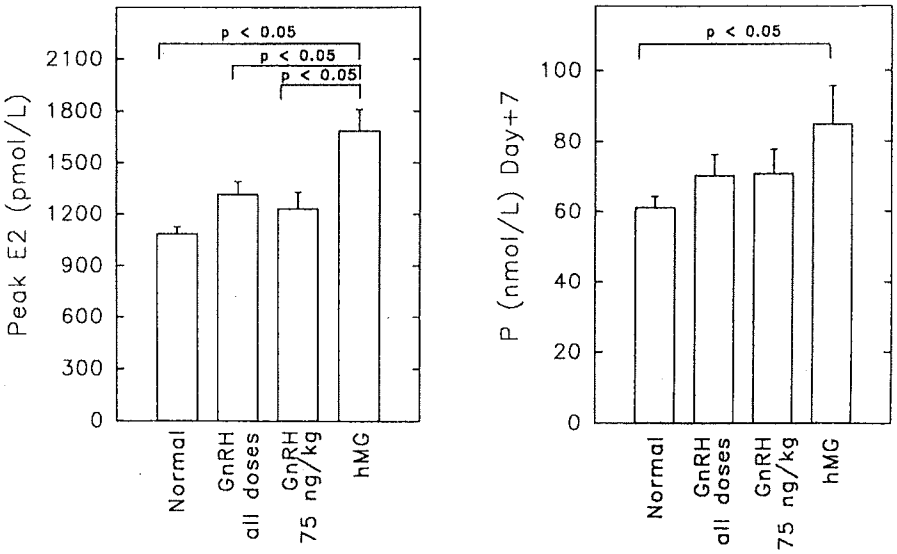

FIG. 2. Mean preovulatory serum E_2 (picomoles per L; *left panel*) and mean P (nanomoles per L) levels 1 week after ovulation or ovulatory hCG treatment (*right panel*) for subjects treated with exogenous gonadotropins (hMG) *vs.* those receiving pulsatile GnRH and normal subjects (n = 87).

those previously reported (18.9–27.9%/cycle and 60.4–63.3%/patient) (6, 16). The ovulatory and conception rates per cycle for pulsatile GnRH in this study were 93% and 29%, respectively, similar to the 89–90% and 27–27.6% ranges reported in previous reviews of iv GnRH treatment (9, 17). While conception rates per cycle were comparable in the two treatment groups, the cumulative chance of conceiving after six cycles of pulsatile GnRH therapy was 96%, which is higher than the 72% after gonadotropin treatment or the 79% reported for the normal population (18). It is possible that the exogenous gonadotropin group included patients with other subtle infertility factors. However, there was no clinical evidence for this, as both groups were screened for male factor and tubal disease. The rate of spontaneous abortion was slightly higher in the pulsatile GnRH group (P = NS), and of note, the viable term pregnancy rate was comparable in the two groups.

The incidence of multiple gestations was higher in the gonadotropin group (14.8%) than with pulsatile GnRH (8.3%), although this was not significantly different. The incidence reported here for patients treated with exogenous gonadotropins is lower than that previously noted for hypogonadotropic patients (24–50%) (5–7), possibly due to a conservative approach to gonadotropin treatment. The overall multiple gestation risk reported previously for hypogonadotropic patients using pulsatile GnRH is approximately 14%, although this complication is more common when higher doses are used (17).

Of note, all higher order multiple gestations in this study were seen only in the exogenous gonadotropin group, presumably a reflection of the greater number of follicles achieved with this therapy. In contrast, all multiple gestations with pulsatile GnRH were twin pregnancies. This may represent an important difference, because of the increased morbidity and mortality associated with higher order multiple gestations (5). A significantly higher number of exogenous gonadotropin cycles resulted in more than two or three dominant follicles, and cycles were cancelled only in the exogenous gonadotropin group. It is striking that even with a conservative approach to ovulation induction with exogenous gonadotropins, multiple folliculogenesis is a frequent event. In contrast, when appropriate doses of GnRH are chosen (75–100 ng/kg), multiple folliculogenesis with pulsatile GnRH is far less common. It is possible that if a more aggressive gonadotropin regimen had been used or a greater number of patients had been studied, a significant difference in multiple gestation risk from pulsatile GnRH would have been more likely.

The risk of severe hyperstimulation with exogenous gonadotropin therapy has been reported to be between 0.008–10%, with most series reporting an incidence of less than 2% (8). However, the risk of severe hyperstimulation appears to have diminished somewhat with the advent of improved clinical monitoring, in particular serum E_2 assays (19). In spite of improved monitoring, however, cases of severe hyperstimulation continue to be frequently reported (20, 21). In contrast, severe ovarian hyperstimulation with pulsatile GnRH has never been described. Interestingly, when using ultrasound rather than bimanual exam for diagnosis, the reported incidence of mild to moderate hyperstimulation with gonadotropin therapy is high (44%), as the bimanual exam in general underestimates ovarian size (22). This suggests that ovarian enlargement is a common result of ovulation induction with exogenous gonadotropins.

Although no cases of severe hyperstimulation were seen in either treatment group in this study, mean luteal phase ovarian size was significantly greater in the exogenous gonadotropin group than in those treated with pulsatile GnRH, presumably a reflection of the increased follicular number and, therefore, increased corpora lutea number. Preovulatory serum E_2 levels, which have been shown to correlate with hyperstimulation risk (23), were supraphysiological in the exogenous gonadotropin group compared to those in our normal population and were significantly higher than those in all GnRH treatment groups. Luteal phase P levels were significantly higher than normal and higher than those in the GnRH groups, although this was not statistically significant. In contrast, preovulatory serum E_2 levels as well as

luteal phase P levels in the pulsatile GnRH groups were not significantly different from those in our normal population, confirming that normal reproductive cycles can be recreated in patients with complete or partial GnRH deficiency.

In our experience, the involvement and discomfort to patients using gonadotropins or pulsatile GnRH is roughly equivalent. While an indwelling iv catheter might appear cumbersome, it is well tolerated, and in most patients' opinions is offset by the decreased need for frequent office visits for monitoring. Because of the apparent improved safety profile of pulsatile GnRH, ovulation induction does not require the intensity of monitoring that is key to the safe administration of exogenous gonadotropins. Therefore, in a therapeutic setting, it has been estimated that the cost of ovulation induction could be considerably reduced with pulsatile GnRH compared with exogenous gonadotropins (9, 24).

Conclusion

Pulsatile GnRH, compared to exogenous gonadotropins, results in high rates of ovulation and conception, a decreased risk of multiple folliculogenesis, higher order multiple gestations, ovarian enlargement, and cycle cancellation. In addition, pulsatile GnRH results in more physiological preovulatory E_2 levels and luteal phase P levels compared to normal values. Because of the improved safety profile, one would also anticipate a reduction in costs because of a decreased need for intensive monitoring. A prospective randomized trial with a carefully matched population will be necessary to further clarify these important issues.

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