European Journal of Obstetrics & Gynecology and Reproductive Biology 168 (2013) 45–48

Contents lists available at SciVerse ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Prospective, randomized comparison between pulsatile GnRH therapy and combined gonadotropin (FSH + LH) treatment for ovulation induction in women with hypothalamic amenorrhea and underlying polycystic ovary syndrome

Sophie Dubourdieu, Thomas Fréour *, Lionel Dessolle, Paul Barrière

Médecine et Biologie de la Reproduction, Hôpital Mère et Enfant, CHU de Nantes, 38 boulevard Jean Monnet, 44093 Nantes cedex, France

ARTICLE INFO

Article history:
Received 4 May 2012
Received in revised form 26 November 2012
Accepted 16 December 2012

Keywords:
Hypothalamic amenorrhea
Polycystic ovary syndrome
Pulsatile GnRH therapy
Ovulation induction

ABSTRACT

Objective(s): To compare the efficacy of pulsatile GnRH therapy versus combined gonadotropins for ovulation induction in women with both hypothalamic amenorrhoea and polycystic ovarian syndrome (HA/PCOS) according to their current hypothalamic status.
Study design: This single-centre, prospective, randomized study was conducted in the Nantes University Hospital, France. Thirty consecutive patients were treated for ovulation induction with either pulsatile GnRH therapy or combined gonadotropins (rFSH + rLH). Frequency of adequate ovarian response (mono- or bi-follicular) and clinical pregnancy rate were then compared between both groups.
Results: Ovarian response was similar in both groups with comparable frequency of adequate ovarian response (73% vs 60%), but the clinical pregnancy rate was significantly higher in the pulsatile GnRH therapy group than in the combined gonadotropin group (46% vs 0%).
Conclusions: HA/PCOS is a specific subgroup of infertile women. Pulsatile GnRH therapy is an effective and safe method of ovulation induction that can be used successfully in these patients.

1. Introduction

Polycystic ovarian syndrome (PCOS) and hypothalamic amenorrhea (HA) are well-defined causes of female infertility. PCOS is the most common cause of anovulation, infertility and hyperandrogenism, affecting 5–10% of women of reproductive age [1,2]. In the majority of cases, clinical hyperandrogenism develops at puberty or shortly after. HA is another common and theoretically reversible form of anovulation, mainly associated with stressors such as low dietary intake and/or intensive physical exercise [3]. Diagnosis of HA requires the exclusion of all other causes of amenorrhea/anovulation such as hyperandrogenism, hyperprolactinemia, thyroid dysfunction, or other systemic diseases. Although HA and PCOS are the most frequent causes of anovulation, only a small number of studies have reported their coexistence in some anovulatory women, suggesting that the ovaries in these HA/PCOS women may be inherently hyperandrogenic but remain quiescent due to low gonadotropins correlated with hypothalamic inactivity [4].

Despite similar hypoestrogenism in HA/PCOS and HA women, clinical, hormonal profiles and pelvic ultrasound examination differ significantly between these two groups, with HA/PCOS women presenting with higher body mass index (BMI), more frequent hyperandrogenism, different bone health markers and higher serum levels of luteinizing hormone (LH) and testosterone than HA women [5]. Over time, these patients may fluctuate between symptoms of HA and PCOS, depending on the status of their hypothalamic function.

Although ovulation induction is theoretically easy in HA patients with the use of gonadotropins or with pulsatile gonadotropin-releasing hormone (GnRH) therapy, these protocols generally lead to inadequate ovarian response in HA/PCOS women, with the same trend towards excessive and multifollicular development, as seen in PCOS women, but not in women with HA alone [6,7]. Thus, the aim of this study was to compare the efficacy of pulsatile GnRH therapy vs a combination of recombinant gonadotropins, i.e. follicle-stimulating hormone (rFSH) + LH (rLH), for ovulation induction in HA/PCOS women according to their current hypothalamic status.

2. Materials and methods

This prospective randomized cohort study was conducted in the Assisted Reproductive Technology (ART) centre of the University Hospital of Nantes, France, between April 2009 and April 2011. All women presenting with HA and underlying PCOS with a history of ovulation induction failure after clomiphene citrate (100 mg/day)

* Corresponding author at: Médecine et Biologie de la Reproduction, Hôpital Mère et Enfant, CHU de Nantes, 38 boulevard Jean Monnet, 44093 Nantes cedex, France. Tel.: +33 2 40 08 43 70; fax: +33 2 40 08 32 28.
E-mail address: thomas.freour@chu-nantes.fr (T. Fréour).

0301-2115/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejogrb.2012.12.016

and/or rFSH alone and/or human menopausal gonadotropins (hMG, Menopur®, Ferring, France) were prospectively included after giving informed consent.

The study was accepted by the ART centre's internal review board. HA was defined as amenorrhea of 6 months or more with a history of weight loss due to low dietary intake and/or intensive physical exercise, after exclusion of other causes of secondary amenorrhea [8]. PCOS was defined using the Rotterdam criteria, with at least two of the following three items: hyperandrogenism or biochemical signs of hyperandrogenism, oligoanovulation or amenorrhea, and presence of polycystic ovary at ultrasound (U/S) [9]. Clinical hyperandrogenism was defined by the presence of hirsutism (modified Ferriman–Gallwey score over 6) and/or acne located in more than two areas. Standard infertility workup was conducted in all patients.

All patients received dydrogesterone (10 mg/day for 10 days). In the event of uterine bleeding, blood sampling for measurement of basal FSH, LH and estradiol (Elecsys, Roche) as well as serum anti-Müllerian hormone (AMH) (Immunotech, Beckman Coulter) was performed on day 2 or 3 after the beginning of the bleeding. In the absence of bleeding, blood sampling was performed 7 days after dydrogesterone withdrawal. Antral follicle count (AFC) was also performed by one single trained operator on day 2 or 3 after menstrual bleeding and all follicles ranging from 2 to 9 mm in mean diameter were considered (Sonosite Titan device®). All women had documented normal TSH, prolactin and 17-OH progesterone levels. For the ovarian area and follicle number, the mean of values recorded for each ovary was used for statistical analysis.

A computer-generated randomization list was used to choose between subcutaneous pulsatile GnRH therapy or combined gonadotropins, i.e. recombinant FSH (rFSH) and LH (rLH), for ovulation induction. In both groups, treatment was initiated on day 2 of the cycle after progestin had induced bleeding or after combined oestrogen–progestin treatment had been administered for 21 days in the case of a previously negative progestin test. After randomization, patients received one of the following two induction protocols for one cycle: Group 1: Pulsatile GnRH therapy with a dose of 15 μg GnRH per pulse (Lutrelef® 3.2 mg, Ferring, France) administered every 90 min subcutaneously (sc) and Group 2: daily sc injection with rFSH (75 IU – Gonal F®, Merck Serono, France) + rLH (75 IU – Luveris®, Merck Serono, France). Ovarian response was monitored regularly with transvaginal ultrasound (Sonosite Titan® device) and serum estradiol (E2), LH and progesterone measurements. The first monitoring was usually performed after 6–7 days of treatment, and repeated every 2–3 days onwards, according to ovarian response. If dominant follicle development did not occur within 9 days of stimulation, the treatment dose was increased to 20 μg/pulse for pulsatile GnRH treatment (Group 1) and by 37.5 IU for rFSH injection (Group 2).

Ovulation was triggered with a single 250 IU recombinant hCG (rhCG) injection (Ovitrelle®, Merck Serono, France) when one ovarian follicle reached 17 mm in diameter. Timed intercourse was scheduled on rhCG injection day, or intrauterine insemination (IUI) was performed 36 h after rhCG injection. All women had luteal phase support with 1500 IU of hCG injection repeated three times, once every 72 h. If more than three leading follicles were seen on ultrasound, rhCG was not injected and no further treatment was administered during the cycle. A pregnancy test was carried out 9 days after the last hCG injection, and if positive, clinical pregnancy was confirmed ultrasonographically 5 weeks later by the detection of a gestational sac and foetal heart activity.

Statistical analysis was performed with Medcalc software, v 11.1.1.0. Proportions were compared with Fisher's exact test. Means were compared with Student's *t*-test. A p value of <0.05 was considered significant.

Table 1
Clinical and hormonal characteristics in the 2 groups of patients. (Results are presented as mean ± standard deviation or as absolute number when appropriate.).

	Group 1 pulsatile GnRH ($n=15$)	Group 2 rFSH + rLH ($n=15$)	p
Age (years)	28.06 ± 2.2	28.66 ± 3.2	
Infertility duration (months)	20.06 ± 7.3	19.66 ± 8.3	
BMI (kg/m^2)	19 ± 0.92	18.9 ± 1.1	
Clinical hyperandrogenism (n)	12	11	
Testosterone (ng/mL)	0.44 ± 0.25	0.39 ± 0.2	
Basal FSH (IU/L)	5.35 ± 1.5	6.52 ± 2.16	
Basal LH (IU/L)	4.94 ± 3.05	5.75 ± 3.55	
Basal estradiol (pg/mL)	29.2 ± 19.5	30.25 ± 17.62	
Serum AMH (μg/L)	10.31 ± 6.79	9.72 ± 7.2	
Ovarian area (cm^2)	4.51 ± 0.97	4.92 ± 1.33	
Antral follicle count (follicles per ovary)	16.17 ± 3.2	15.97 ± 2.5	

3. Results

A total of 30 women were included in the study, 15 receiving pulsatile GnRH therapy (Group 1) and 15 receiving combined gonadotropins (Group 2). The clinical history of each patient was investigated. At a time when no factors predisposing them to HA were present, 15 (50%), 7 (23.3%) and 8 (26.6%) patients presented respectively with a history of oligoamenorrhea, menstrual disturbance (i.e. irregular cycle length >35 days) or regular cycles. Twenty-one women (70%) had taken an oral contraceptive to regulate their menstrual cycle and acne, and 5 (16.6%) had been treated for hirsutism with cyproterone acetate. Treatment with clomiphene citrate up to 100 mg/day for 5 consecutive days (n = 15 patients) and/or FSH alone (n = 19) and/or hMG (n = 5) had previously failed to induce ovulation in all patients.

As expected, the clinical and hormonal characteristics were similar in both groups (Table 1). Mean BMI was comparable to the mean BMI usually observed in HA patients (Table 1). Clinical hyperandrogenism was observed in the majority of the patients (77%), although the mean serum testosterone level was normal (Table 1). The mean serum AMH level was high (9.9 ± 7.1 μg/L), comparable to values usually observed in PCOS patients [10]. Ovarian stimulation parameters and the cancellation rate for excessive ovarian response (26%) were comparable in both groups (Table 2). IUI proportion and semen parameters were comparable in both groups (data not shown). Seven ongoing pregnancies were obtained in the pulsatile GnRH group, whereas no ongoing pregnancy occurred in the gonadotropin group (one biochemical pregnancy). All these pregnancies were singleton, and no miscarriage occurred.

Table 2
Ovarian stimulation parameters and cycle outcome in both groups of patients (NA: not applicable).

	Group 1 pulsatile GnRH ($n=15$)	Group 2 rFSH + rLH ($n=15$)	p
Stimulation duration (days)	11.73 ± 4.25	12.35 ± 3.17	
Cancellation for excessive ovarian response (n)	4	4	
Treatment adjustment (n)	3	7	
Cancellation for absence or inadequate ovarian response (n)	0	2	
Mono or bifollicular ovarian response (n, %)	11 (73.3%)	9 (60%)	
Positive pregnancy test (n, %)	8 (53.3%)	1 (6.7%)	0.01
Clinical ongoing pregnancy (n, %)	7 (46.6%)	0 (0)	0.02
Monofoetal pregnancy (n)	7	NA	NA