ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Pulsatile gonadotropin-releasing hormone therapy in persistent amenorrheic weight-recovered anorexia nervosa patients

Natacha Germain, M.D., Ph.D.,[a,b] Anaïs Fauconnier, M.D.,[a] Jean-Philippe Klein, M.D., Ph.D.,[c,d] Amélie Wargny, M.Sc.,[b] Yadh Khalfallah, M.D., Ph.D.,[a] Chrysoula Papastathi-Boureau, M.D.,[a] Bruno Estour, M.D., Ph.D.,[a,b] and Bogdan Galusca, M.D., Ph.D.[a,b]

[a] Department of Endocrinology, Diabetes, Metabolism and Eating Disorders, University hospital of Saint-Etienne, Saint-Etienne; [b] Eating Disorders, Addictions & Extreme Bodyweight Research Group EA 7423, Jean Monnet University, Saint-Etienne; [c] Department of Histology and Embryology, University Hospital of Saint-Etienne, Saint-Etienne; and [d] Unité de Mixte de Recherche Institut National de la Santé et de la Recherche Médicale 1059, Jean Monnet University, Saint Etienne, France

Objective: To compare hormonal and clinical responses to GnRH pulsatile treatment in weight-recovered anorexia nervosa patients (Rec-AN) with persistent functional hypothalamic amenorrhea (HA) vs. in patients with secondary and primary HA.
Design: Retrospective, observational, ambulatory study.
Setting: University hospital.
Patient(s): Forty-one women: 19 Rec-AN (body mass index >18.5 kg/m^2 without menses recovery), 15 secondary HA without any eating disorders patients (SHA), and 7 primary HA patients (PHA).
Intervention(s): Gonadotropin-releasing hormone pulsatile therapy.
Main Outcome Measure(s): Baseline E_2, LH, and P plasma levels and their changes during induction cycles; ovulation, follicular recruitment, and pregnancies.
Results: The Rec-AN group displayed higher basal E_2 and LH plasma levels after GnRH injection compared with SHA and PHA. Higher E_2 and LH levels were observed during induction cycles in Rec-AN compared with SHA and PHA. Follicular recruitment was higher in Rec-AN. The ovulation rate was higher in Rec-AN compared with PHA but similar to SHA.
Conclusion(s): This study showed increased gonadal status and higher E_2 response to pulsatile GnRH therapy in persistent amenorrheic weight-recovered AN compared with HA from other causes. It suggests that their individual set-point of body weight allowing a fully functional gonadal axis is not reached yet. Specific factors of gonadal inertia in Rec-AN still remain unclear. (Fertil Steril® 2016;■: ■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Anorexia nervosa, hypothalamic amenorrhea, pulsatile GnRH therapy

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/12850-22853

Anorexia nervosa (AN) is an eating disorder affecting mainly women (1, 2). It is characterized by self-starvation leading to noninflammatory undernutrition and hormonal changes (3), such as blunted leptin plasma level, low insulin-like growth factor type 1 (IGF-1) plasma level, low free triiodothyronine (T3) syndrome, and high cortisol plasma level (4). Despite recent modification in the *Diagnostic and Statistical Manual of Mental Disorder* definition (5), AN is also associated with a functional hypothalamic amenorrhea in women, defined by the inability for the hypothalamus to deliver pulsatile GnRH secretion, leading to blunted functioning of the gonadotropic axis (4).

Menses resumption during the weight gain process is still relevant for nutritional recovery monitoring. Unfortunately, weight gain recovery above the lower limits of weight normality associated with normalization of the altered nutritional markers cited above, although indispensable, is not always sufficient to restore the

Received July 30, 2016; revised October 1, 2016; accepted October 24, 2016.
N.G. has nothing to disclose. A.F. has nothing to disclose. J.-P.K. has nothing to disclose. A.W. has nothing to disclose. Y.K. has nothing to disclose. C.P.-B. has nothing to disclose. B.E. has nothing to disclose. B.G. has nothing to disclose.
Reprint requests: Natacha Germain, M.D., Ph.D., Endocrinology Department, University Hospital of Saint-Etienne, Saint Etienne Cedex 2 42055, France (E-mail: natacha.germain@chu-st-etienne.fr).

Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.10.032

gonadotropic function in AN patients (1). An individual set-point of body weight and body composition was indeed suggested (6), but the underlying causes of persistent amenorrhea despite full weight recovery still need to be explained and/or explored (7).

In clinical practice, fertility can be restored in hypothalamic amenorrhea patients using pulsatile GnRH therapy with a pump, to re-establish GnRH pulse (8–11). This medical device, installed either IV or SC, delivers pulsatile doses of GnRH every 90 minutes. Contrary to other assisted reproductive technologies, it replicates normal physiology by stimulating normal secretion of LH and FSH from the pituitary, allowing physiologic maturation of ovarian follicles. The efficacy and safety of this device has been tested in several studies in the past, with cumulative pregnancy rates between 70% and 93% after an average of six cycles of induction, pregnancy rate per cycle between 18% and 45%, and ovulation rate per cycle between 70% and 95% in hypothalamic amenorrhea patients (12–17). Unfortunately, underweight patients were frequently included in those studies, questioning the possible high number of weight nonrecovered AN patients using this assisted reproductive procedure. On the other hand, only a few retrospective studies have been conducted in AN patients. Small numbers and heterogeneity of the studied populations were the main limitations of these trials, mixing indeed sometimes weight-recovered and nonrecovered patients (12, 18, 19). The induction procedure was also different in terms of hormonal pretreatment and using different methods of luteal phase sustaining procedure, sometimes in the same retrospective study. To date, data on hormonal changes and fertility restoration with GnRH treatment in persistent amenorrheic weight-recovered AN are rare. In addition, comparison data on the hormonal response of this entity with primary and secondary hypothalamic amenorrhea not related to eating disorders is also lacking.

The primary purpose of our study was therefore to compare pituitary and gonadal responses to GnRH pulsatile treatment in three well-defined female groups with hypothalamic amenorrhea: [1] weight-recovered AN patients with persistent amenorrhea, [2] patients with secondary hypothalamic amenorrhea with no eating disorders, and [3] patients with primary hypothalamic amenorrhea of other causes. Comparison of the pregnancy success rate among the different groups as a clinical outcome was our secondary purpose.

MATERIALS AND METHODS

Ethics

This was a retrospective, observational, monocentric study. The local institutional research and ethics committee of Saint-Etienne, France approved the study. Data collection continued from August 2001 to March 2013.

Subjects

Forty-one female ambulatory patients with hypothalamic amenorrhea, seeking pregnancy and eligible for pulsatile GnRH therapy in our center, were included in this study (no LH pulse, evaluated by blood sampling every 10 minutes during 4 hours; no polycystic ovary syndrome [PCOS] [20]; strictly normal hysterosalpingogram and normal partner's semen evaluation, interpreted according to recommendations at the time they were performed).

Patients were divided among three groups according to the underlying cause of their hypothalamic amenorrhea, as follows.

Nineteen women with persistent amenorrheic weight-recovered anorexia nervosa (Rec-AN) were included. Weight-recovered was defined as body mass index >18.5 kg/m^2 and no biological markers of undernutrition (free T3, IGF-1, and cortisol). All patients had previous agreement of the psychiatrist in charge of their treatment.

Fifteen patients with primary hypothalamic amenorrhea (PHA), for whom menstruation never started, were also included. Eight of 15 patients tested positive for genetic Kallman syndrome.

Seven patients had secondary hypothalamic amenorrhea (SHA), defined as cessation of menstruation cycles for more than 6 months, but no eating disorder and undernutrition history. In five patients a psychological trauma preceding amenorrhea could be identified (one sexual harassment, two ended a relationship, and two aggressions).

Exclusion criteria were PCOS, tubal obstruction, endometriosis, undernutrition, and sperm abnormalities.

Infusion Pump Procedure

Gonadotropin-releasing hormone pulsatile therapy was administered using a portable SC infusion pump (Zyklomat, Ferring SA) containing 3.2 mg of GnRH (Lutreref, Ferring SA). Frequency and dose were set up according to previously published data (13): 20 μg every 90 minutes during 4 weeks.

No estroprogestative pretreatment was administered to any patient before the pulsatile GnRH therapy. The pump was then placed on the abdomen of the patient for delivering GnRH SC for 4 weeks. The device was maintained during all the induction cycle (defined as pulsatile GnRH therapy for 4 weeks), and no other hormonal treatment was added to trigger ovulation or to support luteal phase. Conception occurred upon intercourse.

Study Design

Each patient underwent the same procedure throughout the study.

At baseline visit, data were gathered on weight, height, and age, as well as from initial hormonal and nutritional assessment (leptin, free T3, IGF-1). Cortisol over 24 hours was recorded, to eliminate other endocrine diseases leading to hypothalamic amenorrhea. Baseline gonadotropin plasma levels (E_2, LH, and FSH) were also measured, as well as LH and FSH response 30 minutes after IV injection of 100 μg of GnRH. Luteinizing hormone pulse was evaluated by blood sampling every 20 minutes during 4 hours.

The SC infusion pump was then placed on the patient, who was educated in managing the device. Frequency and