Efficacy and safety of pulsatile gonadotropin-releasing hormone therapy among patients with idiopathic and functional hypothalamic amenorrhea: a systematic review of the literature and a meta-analysis

Anastasios Tranoulis, Ph.D.,[a] Alexandros Laios, Ph.D.,[a] Andreas Pampanos, Ph.D.,[b] Drakoulis Yannoukakos, Ph.D.,[c] Dimitrios Loutradis, Ph.D.,[d] and Lina Michala, Ph.D.[d]

[a] Department of Obstetrics and Gynaecology, St. James's University Hospital, Leeds Teaching Hospitals, Leeds, United Kingdom; [b] Department of Genetics, Alexandra Hospital, University of Athens, Athens; [c] Molecular Diagnostics Laboratory, INRaSTES, National Center for Scientific Research "Demokritos", Aghia Parasevi; and [d] Department of Reproductive Endocrinology, Alexandra Hospital, University of Athens, Athens, Greece

Objective: To systematically review and appraise the existing evidence in relation to the efficacy and safety of pulsatile gonadotropin-releasing hormone (pGnRH) for the treatment of women with hypothalamic amenorrhea (HA).
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): A total of 35 studies (three randomized and 32 observational) encompassing 1,002 women with HA.
Intervention(s): None.
Main Outcome Measure(s): Primary outcomes: ovulation rate (OvR), pregnancy per ovulatory cycle rate (POR), and live birth per ovulatory cycle rate (LBOR). Secondary outcomes: multiple gestation (MG), ovarian hyperstimulation syndrome (OHSS), and superficial thrombophlebitis (ST) rates. The summary measures were expressed as proportions and 95% confidence intervals (CI).
Result(s): Pulsatile GnRH treatment appears to achieve high OvRs. A trend toward high PORs and LBORs among women with HA is demonstrated. SC pGnRH achieves comparable OvR compared with IV pGnRH. The incidence of OHSS is low and of mild severity. Treatment with pGnRH is associated with low but slightly higher MG rates compared with the general population. IV administered pGnRH is rarely associated with ST.
Conclusion(s): The high OvRs leading to a high rate of singleton pregnancies and the low likelihood of OHSS render the pGnRH treatment modality both effective and safe for the treatment of women with HA of either primary or secondary origin. (Fertil Steril® 2018;109:708–19. ©2017 by American Society for Reproductive Medicine.)
Key Words: Hypothalamic amenorrhea, infertility, pulsatile GnRH, meta-analysis

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/28815-25223

Received October 29, 2017; revised and accepted December 21, 2017; published online March 28, 2018.
A.T. has nothing to disclose. A.L. has nothing to disclose. A.P. has nothing to disclose. D.Y. has nothing to disclose. D.L. has nothing to disclose. L.M. has nothing to disclose.
Reprint requests: Anastasios Tranoulis, Ph.D., Department of Obstetrics and Gynaecology, St. James's University Hospital, Leeds Teaching Hospitals, Beckett Street, Leeds LS9 7TF, United Kingdom (E-mail: tasostranoulis@yahoo.com).

Fertility and Sterility® Vol. 109, No. 4, April 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2017.12.028

Hypothalamic amenorrhea (HA) is defined as the absence or cessation of menses caused by a deficiency in the GnRH pulsatile secretion below a critical range. Primary hypothalamic amenorrhea (PHA) is caused by a developmental insufficiency of GnRH secretion, while secondary hypothalamic amenorrhea (SHA) is a neuroendocrine disorder derived from energy deficit, eating disorders, stress, and excessive exercise in the absence of any organic disorders (1, 2).

Anovulation and infertility are common presenting complaints among women with dysfunctional hypothalamus requiring hormonal therapeutic intervention. Ovulation can be achieved either by FSH administration for follicular maturation, followed by hCG or LH to trigger ovulation, or with pulsatile GnRH, administered either IV or SC by means of a pump (1, 2). GnRH can be administered at different pulse frequencies across the cycle, mimicking physiological ovarian stimulation. The usual doses range between 5–10 μg or 15–20 μg/pulse injected IV or SC, respectively, every 90 minutes (1, 2). Pulsatile GnRH administration leads to a physiological gonadotropin production by the pituitary triggering the development of monofollicular menstrual cycles, thus minimizing the risk of multiple gestation (MG) and ovarian hyperstimulation syndrome (OHSS) (1, 2).

Notably, pulsatile GnRH (pGnRH) is the treatment of choice for HA, favoring ovulation and increasing fertility rates (1, 2). Previous published data suggest that pGnRH is superior to conventional exogenous gonadotropin in achieving ovulation with a lower risk of adverse outcomes. Albeit a simple, efficient, and safe treatment modality, pGnRH has received little attention to date, and it is relatively underused. To ascertain the efficacy of pGnRH, we conducted a systematic review and a meta-analysis of the proportions of women treated with pGnRH administration, who had successful ovulation, conception, delivery of live infants, and adverse outcomes such as MG, OHSS, and superficial thrombophlebitis (ST) per total number of women treated with pGnRH.

MATERIAL AND METHODS

Search Strategy

The present study was carried out according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. A literature search was performed to identify eligible studies from four electronic databases: PubMed, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials CENTRAL. All databases were consulted from inception until October 2017. Eligible studies were retrieved based upon the Boolean search strategy (PICO) in order to describe the patient population (P: hypothalamic amenorrhea), the intervention (I: pGnRH), and the outcome (O: Ovulation OR Pregnancy OR live birth OR adverse outcomes) without defining any comparison (C:/) or study design (S:/). In terms of PubMed searching, a combination of Mesh terms and key words were combined: hypothalamic amenorrhea; primary hypothalamic amenorrhea; secondary hypothalamic amenorrhea; functional hypothalamic amenorrhea; anorexia nervosa; amenorrhea; pulsatile GnRH treatment; pulsatile gonadotropin-releasing hormone treatment; treatment. A similar modified search strategy was conducted for subsequent databases. References of selected studies as well as gray literature were searched for articles not identified by the electronic search, in an attempt to retrieve additional citations.

Inclusion Criteria

The inclusion criteria were [1] confirmed sole diagnosis of PHA or SHA before treatment; [2] studies on the treatment of PHA and SHA with pGnRH; [3] randomized controlled trials (RCTs) and observational studies (OSs); [4] reported data with respect to ovulation rate (OvR); [5] sufficient published data for estimating the pooled proportions and 95% confidence intervals (95% CIs); [6] English language.

Exclusion Criteria

Exclusion criteria included [1] studies irrelevant to treatment of HA with pGnRH; [2] insufficient data for the OvR; [3] case reports, reviews, and small case series of five or fewer patients; [4] repeated or overlapped data; [5] non-English studies.

Literature Search and Data Collection

The eligible articles were retrieved following a two-step process. First, the titles and abstracts of the articles were screened for tabulation eligibility by two independent reviewers (A.T., A.L.) and full manuscripts were identified. In case of duplicates, the most recent or complete article was selected. If there was any disagreement, consensus was sought with senior reviewers (L.M., D.L.). The selection process for included studies is shown in Supplemental Figure 1.

Quality Assessment

The Methodological Index for Non-Randomized Studies (MINORS) was used to assess the quality of OS (Supplemental Fig. 2) (3). RCTs were evaluated using the modified Jadad score, which briefly assesses the description of studies as randomized along with details of the randomization and the description and details of the double-blind process, in addition to information in terms of withdrawals and allocation concealment (Supplemental Table 1) (4). Two reviewers (A.T., A.L.) evaluated the yielded articles accordingly. Any disagreements were resolved by consensus or arbitration by two senior reviewers (L.M., D.L.).

Statistical Analysis

For the analysis of outcomes, we carried out a meta-analysis of the proportions of women treated with pGnRH administration who had successful ovulation, conception, delivery of live infants, and adverse outcomes (MG, OHSS, and ST) per total number of women treated with pGnRH. Subsequently, a separate subgroup analysis according to the route of administration (IV or SC) and the type of HA (PHA or SHA) was carried out. We computed the logarithm of the ratio and its corresponding standard error for each of the studies. A meta-analysis with inverse-variance weighting was conducted using a random-effects model. Forest plots were created for each