Side effects of pulsatile GnRH therapy for induction of ovulation

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EXPERT REVIEWS

"Since 1980, pulsatile application of gonadotropin-releasing hormone has been used clinically for induction of ovulation and to accrue important information on the physiology and pathophysiology of the menstrual cycle."

Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus in a pulsatile fashion. The average frequency of one pulse every 90–120 min was first observed in ovariectomized rhesus monkeys and later demonstrated in hypogonadal women and during the proliferative and periovulatory phases of the human menstrual cycle. Furthermore, it has been demonstrated that intermittent stimulation of the pituitary gland by GnRH is required for maintaining gonadtropin secretion and that continuous administration is inefficient in this regard. These observations, and the additional demonstration that in primates the feedback effects of estrogens on luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion occur at the level of the pituitary gland with hypothalamic GnRH playing a permissive role in this respect, are the basis of pulsatile GnRH therapy [1–4].

Since 1980, pulsatile application of GnRH has been used clinically for induction of ovulation and to accrue important information on the physiology and pathophysiology of the menstrual cycle. Furthermore, this procedure has been demonstrated to be safe and efficacious in the treatment of infertility in women with GnRH deficiency, such as hypothalamic and hyperprolactinemic amenorrhea [5–8]. Selection of patients for pulsatile therapy based on pathophysiology represents the most critical factor for success of this type of therapy. Therefore, the pathophysiological basis for its application will be described briefly.

Hypothalamic amenorrhea

Hypothalamic amenorrhea, the second most frequent cause of ovarian failure in reproductive-age women, is caused by the reduction of pulsatile hypothalamic GnRH release [4,9,10]. Functionally these patients may be viewed as prepubertal.

Hypothalamic ovarian failure represents a pathophysiological continuum extending from corpus luteum insufficiency to severe primary amenorrhea based on the extent of reduction of pulsatile GnRH secretion, irrespective of the underlying etiology [4,7,9]. It is characterized by low-to-normal LH and FSH levels, and normal prolactin and androgen concentrations in serum. The extent of impairment of hypothalamic GnRH release can be assessed clinically by the response to administration of gestagen, clomiphene and GnRH. The gestagen test is performed by oral administration of medroxyprogesterone-acetate 10 mg for 10 days. The test is designated positive when vaginal bleeding occurs within 10 days after the last gestagen dose. The clomiphene test is started on day 3–5 after gestagen-induced bleeding with clomiphene citrate 100 mg administered daily for 5 days. The clomiphene test is positive when vaginal bleeding starts within 2–3 weeks after the last intake of clomiphene. The GnRH test is of value in gestagen-negative patients. Only 100 µg of GnRH are administered intravenously and blood samples are taken at various time intervals for up to 180 min to determine serum levels of LH and FSH. Based on the findings of these functional tests, hypothalamic amenorrhea can be graded from grade 1 to 3.

Grade 1 hypothalamic amenorrhea is diagnosed in the presence of both positive gestagen and clomiphene tests. grade 2 hypothalamic amenorrhea is diagnosed when a positive gestagen test is followed by a negative clomiphene test. A negative

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gestagen test mandates an additional GnRH test, performed with the bolus administration of 100 µg of GnRH, to further differentiate between grades 3a–c hypothalamic amenorrhea. An adult-like pituitary response to a GnRH bolus, where the rise of FSH exceeds that of LH, defines grade 3a hypothalamic amenorrhea. A prepubertal response to GnRH stimulation, that is, a rise of LH and FSH to the same extent, is found in grade 3b hypothalamic amenorrhea. Absence of a LH and FSH rise in response to GnRH bolus administration characterizes grade 3c hypothalamic amenorrhea.

Pulsatile GnRH therapy

For pulsatile administration of GnRH, a variety of infusion pumps have been developed and used over the last three decades. The Zyklomat pump, distributed by Disetronic in conjunction with the Zyklomat pulse set (Ferring Arzneimittel GmBH), is the infusion pump used most frequently for the pulsatile administration of GnRH at selectable pulse amplitudes and frequencies.

In women suffering from hypothalamic amenorrhea, pulsatile GnRH therapy resembles initiation of puberty, and results in follicular maturation, ovulation and corpus luteum formation [8,9,11]. In favorable couples with hypothalamic disturbance as the only cause of infertility, a pregnancy rate comparable to that of normal healthy couples can be achieved. As demonstrated by our group and several other authors, the pregnancy rate per treatment cycle is 25%, while the mean number of cycles to obtain a pregnancy is 2.8 ± 1.7. The miscarriage rate is 8.2% and the multiple pregnancy rate is 8.8% [8,11,12].

Pulsatile GnRH also constitutes an alternative treatment for infertility in patients with hyperprolactinemia who are unresponsive to, or do not tolerate, dopamine agonists [5,13,14].

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When pulsatile GnRH therapy was first used clinically, the application of GnRH was carried out via intravenous catheters. With the administration of GnRH 5–20 µg per pulse, depending on the grade of hypothalamic amenorrhea, a dose was used that was considered to be the minimal effective dose in stimulating the pituitary gonadotrophs by exogenous GnRH, leading to a physiological pituitary and ovarian response resulting in mono-ovulation [8,9,11,15–17].

To avoid possible side effects of long-term intravenous administration, such as infections or local venous thrombosis, pulsatile GnRH therapy is now performed mainly via administration into the subcutaneous fat tissue of the lower abdominal wall. For this route, dosages between 10 and 30 µg/pulse are necessary to induce ovulation [6–8]. However, delayed resorption of GnRH from the subcutaneous fat tissue may sometimes result in insufficient serum levels of GnRH for adequate stimulation of the pituitary gonadotrophs. In these patients, ovulation and normal luteal function can often be obtained by reverting to the intravenous application of GnRH at the same dose.

Continuation of pulsatile administration of GnRH throughout the luteal phase results in normal luteal function, as indicated by the length of the luteal phase, serum progesterone levels and conception. Frequency of pulsatile GnRH administration during the luteal phase can be reduced to one pulse every 120 min, reducing drug use and costs [8].

Side effects

Side effects can be classified into complications resulting from the application of pulsatile GnRH and adverse effects resulting from erroneous indications.

Complications of pulsatile GnRH application

Since there is a dose–response relationship between the dose of GnRH per pulse and the pituitary–ovarian response, excessive doses will result in mild overstimulation and potentially multiple pregnancies [7,8,11]. It has been suggested that this may occur preferentially when higher doses of human chorionic gonadotropin are administered too early for luteal support. The same holds true for the first treatment cycle in women with secondary hypothalamic amenorrhea, who usually present with a low-grade disturbance (grades 1–3a) [5–8,11,18,19]. In these patients with less-impaired hypothalamic and, thus, gonadotrophic and ovarian function, a number of follicles have usually gained a certain degree of morphological and functional maturity, which allows prompt growth and rapidly increased estradiol secretion as soon as the pulsatile administration is initiated [7]. The first GnRH pulses impinge upon filled pituitary gonadotrophin stores and the resulting supraphysiological gonadotrophin pulses override the mechanisms of monofollicular selection. In these cases, the follicular phase of GnRH-induced cycles is usually shorter, reflecting the presence of a prestimulated cohort of follicles [4–8]. If pulsatile GnRH at the same dose level is uninterruptedly continued into the next cycle, overstimulation does not recur and mono-ovulation ensues [4,8,20]. Thus, in patients with grade 1–3a hypothalamic ovarian failure, the risk of multiple ovulation and pregnancy is usually limited to the initial cycle, and may be effectively prevented by ovarian suppression using oral contraceptives immediately prior to the initiation of treatment.

Infections and local allergic reactions around the subcutaneous or intravenous located needle are possible complications of pulsatile GnRH therapy, and can be prevented by adhering to sterile procedures and by changing the needle once or twice a week. Drug-related side effects, such as development of antibodies, have not been observed so far.

Complications due to inappropriate application

Erroneous indication of pulsatile GnRH treatment can similarly lead to adverse effects in women who initially present with typical signs and symptoms of hypothalamic amenorrhea, but

suffer from a discrete form of hyperandrogenemia, which may be combined with hypothalamic failure. This was suspected [21] and systematically demonstrated recently by our group [22]. Initially, all these patients respond to pulsatile GnRH therapy with ovulation and corpus luteum formation. However, during continuation of treatment, these patients develop an increase in LH and the LH/FSH ratio, as well as a progressive rise in serum testosterone levels, resulting in hyperandrogenemia. These signs are accompanied by the development of polycystic ovaries and cessation of follicular maturation. This may occur quickly within one or two cycles of pulsatile GnRH administration. This observation strongly suggests that, in these patients, hyperandrogenemia does not originate within the hypothalamus, but rather within the ovary, the pituitary gland, or both of these sites.

By definition, pulsatile GnRH therapy cannot be effective when the cause of ovarian failure resides within the pituitary gland, such as in Sheehan's syndrome or in some rare cases of hemochromatosis or hypophysitis. In such cases, however, pulsatile GnRH administration may be used for differentiation between the hypothalamic and pituitary origin of the disturbance.

Summary

Pulsatile administration of GnRH by means of a portable pump is an efficient and practical method for the induction of ovulation as a treatment of infertility in hypothalamic amenorrhea. It represents a replacement therapy based on physiological observations. Since the feedback mechanisms between the ovary and pituitary gland remain intact, it is associated with a very low risk of multiple follicular development and multiple pregnancies. However, the results obtained with this method are critically dependent upon the correct selection of patients as far as the diagnosis of hypothalamic amenorrhea is concerned. If this is the case, pulsatile GnRH therapy is safe, associated with a very low risk of multiple pregnancy and, therefore, has to be considered as the therapy of choice in hypothalamic amenorrhea.

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