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GnRH agonist and antagonist: Options for endometriosis pain treatment

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OPTIONS FOR ENDOMETRIOSIS PAIN TREATMENT

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Basic science research into the mechanism of the development of endometriosis, its persistence and resulting pain has begun to improve our understanding of how various therapeutic options work. While none of the available treatments resolves the underlying disease process, there are a growing number of alternatives (1,2,3). One of the more recent classes of medical options includes the GnRH agonist and antagonists. While at present this class of medical options is the most expensive and involved in implementation, they prove invaluable in terms of offering an aggressive, successful alternative for many patients. Furthermore, they may act directly on endometrial lesions in a therapeutic manner. This discussion will be oriented toward endometriosis pain management, but many of the medical manipulations may be therapeutic for infertility treatment as well if only by preventing the need for aggressive or emergency surgical management of endometriosis, especially in young women.

Pain symptomatology and American Society of Reproductive Medicine (ASRM) staging (4) or number of endometrial lesions have long been known to show no specific correlation (5,6). Yet, up to 60% of women with dysmenorrhea and 40-50% of women with dyspareunia have endometriosis (7). Thus, assessing improvement on an objective scale by second look laparoscopy may not be as relevant as the clinical measure of pain relief, though it has been utilized in double blind studies (8,9,10,11,12,13). Hormonal suppressive treatment, while effective for pain management, has no specific effectiveness on endometriomas or pelvic adhesions.

Though the initiation of GnRH agonist therapy may dictate laparoscopic documentation of endometriosis (14), second look laparoscopy is not a necessary part of clinical practice. In particular, because of the severity of side effects with GnRH agonists, specific treatment goals, as related to quality of life are important to maximize individual therapeutic success. GnRH agonist or antagonist treatment is usually not considered a first line option for treatment of endometriosis pain (14). Cost as well as side effect profile dictate the use of progestins, whether by oral, IM or IUD use, or oral contraceptives for ovarian suppression as the first line therapy. However, according to the ACOG Committee Opinion empiric GnRH agonist treatment may be offered to patients older than 18 years. If pain subsides, then an empiric diagnosis of endometriosis can be made (14).

GnRH agonists are potent down regulators of pituitary function, increasing initial release then depletion of gonadotropin FSH and LH (15). With regard to endometriosis, they are believed to function by creating an estrogen deficient state by about 2 weeks after the initiation of therapy (16). There is growing scientific evidence that GnRH agonists may have direct action on ovarian steroidogenesis independent of their action on the pituitary and direct effects on endometrial implant growth. Recent laboratory data utilizing biopsy specimens of ectopic endometrium from 16 women with untreated endometriosis confirmed direct action of GnRH agonists on ectopic endometrial cells (17,18). GnRH agonist (leuprolide acetate) exposed cells showed increased apoptosis with decreasing release of promitogenic cytokines such as Interleukin-1 βeta (IL-1β) and Vascular Endothelial Growth Factor (VEGF), both felt to be related to the growth of endometriosis. These effects were reversed by the addition of antide, a GnRH antagonist. The vascular

endothelial growth factor (VEGF) family of angiogenic molecules is involved in general angiogenesis.

Recent data suggests that VEGF may be involved in maintenance of endometriosis (19,20). Immunological factors working through Interleukin 1β [IL-1 β] may act as growth factors as well as protecting cells from apoptotic demise. Both have been measured as elevated in the peritoneal fluid of women with endometriosis [21]. Furthermore, GnRH receptors have been identified in ectopic endometrium (22) suggesting that GnRH may be a direct regulator of endometriosis growth. Iwabe et al demonstrated changes in Interleukin-6 (IL-6) concentration in patients with ovarian endometriomas following laparoscopic removal in 13 patients as well as with GnRH agonist (Buserelin) pre-surgical treatment in 9 patients (23). Matsuzaki et al found estrogen receptor alpha (ERa) mRNA levels decreased in endometriomas after long term GnRH agonist treatment but not ER beta (ER β) mRNA levels (24). Others have demonstrated localized changes secondary to GnRH agonist therapy whether in enzyme levels (25) or apoptosis (26). These actions of GnRH would explain in part the regression of endometrial lesions seen following GnRH agonist therapy (17) as related to more than just the induced hypoestrogenic state.

GnRH agonist therapy also influences eutopic endometrium function in patients with endometriosis either as a consequence of the induced hypoestrogenic state (27) or by direct action such as demonstrated by Wang et al (28). The studies imply an autocrine – paracrine action on local GnRH receptors within endometrium or ectopic endometrial tissue.

The initial action of GnRH agonists is to cause a flare of pituitary FSH and LH which may result in an exacerbation of endometriosis pain due to the ovarian stimulation. Within two weeks, the pituitary gonadotropins are exhausted and an estrogen deficient state is obtained due to the lack of continued ovarian stimulation (29). Concern regarding this initial pain exacerbation dictates beginning treatment in the luteal phase of the cycle when the ovary is less primed for stimulation.

The importance of this initial flare effect of GnRH agonists has been evaluated. Short term endometriosis response to GnRH agonist treatment, in this case leuprolide 3.75mg, was monitored. Miller found an increase in endometriosis associated pain at 2 and 4 weeks when the GnRH agonist was given in the early follicular phase (30). Gelety et al confirmed an exaggeration in the flare effect when the agonist was given in the early follicular phase as opposed to the late follicular phase (31). Furthermore, Meldrum et al demonstrated that pituitary suppression was achieved more rapidly when GnRH agonist treatment was begun in the mid luteal phase (32). Most studies document no increase in pain after the first month of therapy (33,34).

The rapid induction of an estrogen deficient state as profound as surgical menopause, accounts for most of the side effects related to GnRH agonist therapy (see table I). Up to 95% of patients experienced menopausal symptoms, the most common of which are hot flashes and insomnia (35,35a,35b,36,37). Other symptoms less frequently noted include vaginal dryness, mood changes, and headache. Lipid changes include a decrease in

HDL and increase in LDL. These symptoms as well as the therapeutic effects occur for the most part regardless of the GnRH agonist utilized (Table II).

Concern regarding bone loss has become the rate limiting change related to GnRH agonist therapy (14). Average bone loss of 4 to 6% detected after 6 months of GnRH agonist therapy (38,39,40) appears to be related to the hypoestrogenic state (41). While most people appear to regain bone density loss as estrogen levels return to normal with discontinuation of therapy, most authors have suggested a 6 month limit to GnRH agonist therapy (42,43,44). Variability related to the reversibility of bone loss may be due to difference in the agonist utilized, the population studied (diet, lifestyle etc.), patient age (i.e. prior to attainment of peak BMD) or variability in bone mineral density as suggested by Pierce et al (45) and Matsuo (46).

The concept of addback therapy with GnRH agonist treatment was initiated to help temper some of the hypoestrogenic side effects, in particular bone loss. The “estrogen threshold hypothesis” of Barbieri (47) suggested that there was a specific estrogen threshold below which endometriosis was not stimulated, but hot flashes and bone loss were controlled. Titration of the specific hypoestrogenic level while possible with nasal GnRH agonist (personal observation), is not easily achieved with current intramuscular GnRH agonists on the market.

The concept of adding back small quantities of estrogen to ease symptoms, but not compromise treatment efficacy, assumes that an estrogen threshold is constant for most

women. Multiple regimens have been described including estrogen in the form of Premarin 0.625mg or estradiol 1mg to progestins, norethindrone acetate in doses from 2.5mg to 10mg daily and other progestins (48,49,50). Biphosphonates have been added as well (51,52)(Table III). All have shown adequate safety profiles with regard to bone maintenance for up to one year of GnRH agonist use. Equivalent clinical efficacy has been shown with 6 months treatment of GnRH agonist with or without the use of addback therapy without compromising pain relief (40,44,49,53).

However, while not all patients experience vasomotor symptom relief with addback therapy, many find significant changes that make the treatment tolerable (54). Adverse effects of the addback treatment are more prevalent with higher doses. Premarin in a dose of 1.25mg caused women to discontinue treatment to due to pain recurrence (49). Androgenic side effects were induced with norethindrone acetate in a dose of 10mg per day (51). Calcium supplementation is essential as part of a bone maintenance program. Bone density measurement is suggested as part of appropriate follow-up to long term GnRH agonist and addback therapy (greater than one year).

Studies have been done with all of the different GnRH agonists available on the market. Although the various formulations are delivered by different routes of administration and different dosages, ovarian suppression is produced by all with little difference in side effects or efficacy (1,3,55,56).

Pain relief efficacy studies comparing GnRH agonists with danazol, the previous gold standard, or placebo, have been significant. When compared to placebo, leuprolide acetate was highly effective in a 6 month trial (35). Studies comparing various GnRH agonists with danazol, all have shown equivalent pain relief (8,10,11,12,55,56,57,58,59).

GnRH Antagonists

GnRH antagonists are now utilized routinely as part of controlled ovarian hyperstimulation protocols for assisted reproduction and fertility treatments. GnRH antagonists work by competitive blocking of pituitary GnRH receptors (3,60). Their action onset is immediate, time related and reversible. There is no initial flare of gonadotropins either before or after the onset of action. But unlike GnRH agonists, gonadotropins are not depleted though the similar end effect of a hypoestrogen state is achieved (61).

Recent laboratory studies comparing the effects of GnRH agonists with GnRH antagonists on eutopic endometrial cells in women with and without endometriosis showed no direct effects from the antagonists as opposed to the agonists which demonstrated increased apoptosis and decreased cytokines (17). Interestingly, the addition of a GnRH antagonist blocked the down regulation effects of the GnRH agonist on the eutopic endometrial tissue from both endometriosis patients and controls supporting the thesis that direct effects of GnRH agonists in vitro are probably mediated by local GnRH receptor interaction.

Most available clinical forms of GnRH antagonists offer short term (daily or three day) dosing as part of infertility treatment. While theoretically GnRH antagonists should be applicable to endometriosis treatment, as yet few studies have been published. Recent work by Kupker et al (62) utilized subcutaneous injections of a GnRH antagonist (cetrorelix) in 15 patients with pain related to endometriosis. A 3mg once weekly dose over 8 weeks was utilized. Serum estradiol levels ranged around 50 pg/mL during therapy. All patients were symptom free during the treatment period. Subsequent laparoscopy confirmed regression in 60% of cases (9/15) with a significant decline in stage of endometriosis from stage III to stage II.

Based on this, Donnez et al (63) (reported on a dose finding study for a GnRH antagonist, cetrorelix, given over a period of 8 weeks in the treatment of endometriosis. Sixty women with laparoscopy proven endometriosis and moderate to severe symptoms were included in the 8 week trial. Weekly or bi-weekly doses of cetrorelix, 5 mg or 10 mg, were utilized. All resulted in a rapid decrease in endometriosis symptoms by 4 weeks of treatment and the effect continued until 16 weeks based on pain and dysmenorrhea scores. Treatment was well tolerated except for one local injection site irritation. As the authors note, the absence of a flare effect with treatment initiation allows for dose free intervals to be interspersed without risk of exacerbation if retreatment is postponed until symptoms recur. This may allow for an interesting approach to treatment. Development of GnRH antagonist with long term action may be of use for such treatments and is supposedly in progress.

There is recent research regarding a second type of GnRH, GnRH II which occurs throughout peripheral tissues in the female reproductive tract including the placenta, endometrium and granulosa cells of the ovary as well as central nervous system. According to studies by Morimoto et al (64) levels of GnRH II mRNA were lower in endometrial and endometriotic tissue of women with endometriosis than in those without endometriosis. Since the effect of GnRH II is anti-proliferative and anti-inflammatory, its decreased presence in patients with endometriosis suggests another deficient protective mechanism leading to disease development. The addition of GnRH antagonists (antide) blocked GnRH I and GnRH II action in this study, suggesting a specific local effect of GnRH antagonists that may be therapeutic beyond the blocking of pituitary GnRH I.

Conclusion

Treatment with a GnRH agonist does provide proven pain relief in 80-90% of women with documented endometriosis, but medical treatment is suppressive therapy, not extirpative therapy (65) and pain does recur. Though recent evidence suggests a direct effect of GnRH agonist on endometriosis lesions, the addition of medical treatment to conservative surgery pain management has shown extended relief when employed for 6 months or more (65,66).

GnRH agonist therapy has proven efficacious in the treatment of pain related to endometriosis. The addition of immediate addback therapy as well as preventing bone loss, appears to improve compliance and tolerability without sacrificing the therapeutic aim

of pain relief. In this combination, GnRH agonist therapy deserves consideration as first line therapy for proven endometriosis pain relief. Further development of long acting GnRH antagonists for endometriosis treatment deserves attention due to the immediacy of onset, ease of reversibility and lack of pain increase (flare) with utilization.

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Table I. Side Effects of GnRH Agonists

- Hot flashes (80%-90%)
- Sleep disturbances (60%-90%)
- (30%) Vaginal dryness
- Joint pain (30%)
- Breakthrough bleeding (20%-30%)
- Headaches (20%-30%)
- Mood change (10%)
- Bone loss (↓ bone density 5%-6%)
- Adverse lipid changes (↑ LDL, ↓ HDL)

Estimates of prevalence are a composite from published clinical trials (34,35,38)

Modified from Mahutte NG and Arici A. Obstet Gynecol Clin N Am 2003;30:133-150 (3)