



Thomas Jefferson University
Jefferson Digital Commons

Department of Obstetrics and Gynecology Faculty
Papers

Department of Obstetrics and Gynecology

November 2006

GnRH agonist and antagonist: Options for endometriosis pain treatment

Frances R. Batzer

Thomas Jefferson University, leem@womensinstitute.org

[Let us know how access to this document benefits you](#)

Follow this and additional works at: <http://jdc.jefferson.edu/obgynfp>

 Part of the [Obstetrics and Gynecology Commons](#)

Recommended Citation

Batzer, Frances R., "GnRH agonist and antagonist: Options for endometriosis pain treatment " (2006). *Department of Obstetrics and Gynecology Faculty Papers*. Paper 3.
<http://jdc.jefferson.edu/obgynfp/3>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Obstetrics and Gynecology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

1

2

3

4 **GnRH AGONIST AND ANTAGONIST:**

5 **OPTIONS FOR ENDOMETRIOSIS PAIN TREATMENT**

6

7

8 Frances R. Batzer, MD, MBE

9

10

11

12

13

14

15

16

17

18 Reprint Requests: Frances R. Batzer, MD, MBE, 815 Locust Street, Philadelphia PA

19 19107, 215-922-2206, 215-922-3777 (FAX).

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

32

33 Pain symptomatology and American Society of Reproductive Medicine (ASRM) staging
34 (4) or number of endometrial lesions have long been known to show no specific correlation
35 (5,6). Yet, up to 60% of women with dysmenorrhea and 40-50% of women with
36 dyspareunia have endometriosis (7). Thus, assessing improvement on an objective scale
37 by second look laparoscopy may not be as relevant as the clinical measure of pain relief,
38 though it has been utilized in double blind studies (8,9,10,11,12,13). Hormonal
39 suppressive treatment, while effective for pain management, has no specific effectiveness
40 on endometriomas or pelvic adhesions.

41

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

52

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

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

67

68 Recent data suggests that VEGF may be involved in maintenance of endometriosis
69 (19,20). Immunological factors working through Interleukin 1 β [IL-1 β] may act as growth
70 factors as well as protecting cells from apoptotic demise. Both have been measured as
71 elevated in the peritoneal fluid of women with endometriosis [21]. Furthermore, GnRH
72 receptors have been identified in ectopic endometrium (22) suggesting that GnRH may be
73 a direct regulator of endometriosis growth. Iwabe et al demonstrated changes in
74 Interleukin-6 (IL-6) concentration in patients with ovarian endometriomas following
75 laparoscopic removal in 13 patients as well as with GnRH agonist (Buserelin) pre-surgical
76 treatment in 9 patients (23). Matsuzaki et al found estrogen receptor alpha (ER α) mRNA
77 levels decreased in endometriomas after long term GnRH agonist treatment but not ER
78 beta (ER β) mRNA levels (24). Others have demonstrated localized changes secondary
79 to GnRH agonist therapy whether in enzyme levels (25) or apoptosis (26). These actions
80 of GnRH would explain in part the regression of endometrial lesions seen following GnRH
81 agonist therapy (17) as related to more than just the induced hypoestrogenic state.

82

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

88

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

95

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

105

106 The rapid induction of an estrogen deficient state as profound as surgical menopause,
107 accounts for most of the side effects related to GnRH agonist therapy (see table I). Up to
108 95% of patients experienced menopausal symptoms, the most common of which are hot
109 flashes and insomnia (35,35a,35b,36,37). Other symptoms less frequently noted include
110 vaginal dryness, mood changes, and headache. Lipid changes include a decrease in

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

113

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

123

124 The concept of addback therapy with GnRH agonist treatment was initiated to help temper
125 some of the hypoestrogenic side effects, in particular bone loss. The “estrogen threshold
126 hypothesis” of Barbieri (47) suggested that there was a specific estrogen threshold below
127 which endometriosis was not stimulated, but hot flashes and bone loss were controlled.

128 Titration of the specific hypoestrogenic level while possible with nasal GnRH agonist
129 (personal observation), is not easily achieved with current intramuscular GnRH agonists
130 on the market.

131

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

134 women. Multiple regimens have been described including estrogen in the form of Premarin
135 0.625mg or estradiol 1mg to progestins, norethindrone acetate in doses from 2.5mg to
136 10mg daily and other progestins (48,49,50). Biphosphonates have been added as well
137 (51,52)(Table III). All have shown adequate safety profiles with regard to bone
138 maintenance for up to one year of GnRH agonist use. Equivalent clinical efficacy has
139 been shown with 6 months treatment of GnRH agonist with or without the use of addback
140 therapy without compromising pain relief (40,44,49,53).

141
142 However, while not all patients experience vasomotor symptom relief with addback
143 therapy, many find significant changes that make the treatment tolerable (54). Adverse
144 effects of the addback treatment are more prevalent with higher doses. Premarin in a dose
145 of 1.25mg caused women to discontinue treatment to due to pain recurrence (49).
146 Androgenic side effects were induced with norethindrone acetate in a dose of 10mg per
147 day (51). Calcium supplementation is essential as part of a bone maintenance program.
148 Bone density measurement is suggested as part of appropriate follow-up to long term
149 GnRH agonist and addback therapy (greater than one year).

150
151 Studies have been done with all of the different GnRH agonists available on the market.
152 Although the various formulations are delivered by different routes of administration and
153 different dosages, ovarian suppression is produced by all with little difference in side
154 effects or efficacy (1,3,55,56).

155

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

160

161 **GnRH Antagonists**

162

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

169

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

177

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

187

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

199

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

210

211 **Conclusion**

212

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

219

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

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

227 **References**

228

- 229 1. Lessey, B. Medical management of endometriosis and infertility. *Fertil Steril*
230 2000;73:1089-96
- 231 2. Emmi AM. The use of GnRH agonists in the medical therapy of endometriosis in
232 the woman with pain. *Seminars in Reprod Endocrin* 1993;11:119-26
- 233 3. Mahutte NG and Arici A. Medical management of endometriosis-associated pain.
234 *Obstet Gynecol Clin N Am* 2003;30:133-50
- 235 4. American Society for Reproductive Medicine. Revised American Society for
236 Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817-21
- 237 5. Fedele L, Parazzini F, Bianchi S, et al. Stage and localization of pelvic
238 endometriosis and pain. *Fertil Steril* 1990;53:155-58
- 239 6. Vercellini P, Tespidi L, De Giorgi O, et al. Endometriosis and pelvic pain: relation to
240 disease stage and localization. *Fertil Steril* 1996;65:299-304
- 241 7. Eskenazi B, Warner M, Bonsignore L, et al. Validation study of nonsurgical
242 diagnosis of endometriosis. *Fertil Steril* 2001;76:929-35
- 243 8. Henzl MR, Corson SL, Moghissi K, et al. Administration of nasal Nafarelin as
244 compared with oral danazol for endometriosis: a multicenter double-blind comparative
245 clinical trial. *N Engl J Med* 1998;318:485-89
- 246 9. Telimaa S, Puolakka J, Ronnberg L, et al. Placebo-controlled comparison of
247 danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis.
248 *Gynecol Endocrinol* 1987;1:13-23

- 249 10. Shaw RW. An open randomized comparative study of the effect of goserelin depot
250 and danazol in the treatment of endometriosis: Zoladex Endometriosis Study Team. *Fertil*
251 *Steril* 1992;58:265-72
- 252 11. Wheeler JM, Knittle JD, Miller JD. Depot leuprolide versus danazol in treatment of
253 women with symptomatic endometriosis. I. Efficacy results. *Am J Obstet Gynecol*
254 1992;167:1367-71
- 255 12. Rock JA, Truglia JA, Caplan RJ. Zoladex (goserelin acetate implant) in the
256 treatment of endometriosis: a randomized comparison with danazol. The Zoladex
257 Endometriosis Study Group. *Obstet Gynecol* 1993;82:198-205
- 258 13. Bulletti C, Flamigni C, Polli V, et al. The efficacy of drugs in the management of
259 endometriosis. *J Am Assoc Gynecol Laparosc* 1996;3:495-501
- 260 14. ACOG Committee on Adolescent Health Care. Committee Opinion. Endometriosis
261 in Adolescents. ACOG Committee Opinion No. 310. *Obstet Gynecol* 2005;105:921-27
- 262 15. Conn PM, Staley D, Jinnar H. Molecular mechanisms of gonadotrophin-releasing
263 hormone action. *J Steroid Biochem* 1987;23:703-10
- 264 16. Hurst BS, Schlaff WD. Treatment options for endometriosis. *Infertility and*
265 *Reproductive Medical Clinics of North America*. 1992;3:645-55
- 266 17. Meresman GF, Bilotas MA, Lombardi E, Tesone M, et al. Effect of GnRH
267 analogues on apoptosis and release of interleukin-1 β and vascular endothelial growth
268 factor in endometrial cell cultures from patients with endometriosis. *Hum Reprod*
269 2005;18:1767-71

- 270 18. Meresman GF, Buquet RA, Bilotas M, et al. Gonadotropin-releasing hormone
271 agonist (GnRH-a) induces apoptosis and reduces cell proliferation in eutopic endometrial
272 cultures from women with endometriosis. *Fertil Steril* 2003;80(Suppl. 2):702-7
- 273 19. Mc Laren J. Vascular endothelial growth factor and endometriotic angiogenesis.
274 *Hum Reprod Update* 2000;6:45-55
- 275 20. Donnez J, Smoes P, Gillerot S, et al. Vascular endothelial growth factor (VEGF) in
276 endometriosis. *Hum Reprod* 1998;13:1686-90
- 277 21. Wu HN, Wu MY, Yang YS. Peritoneal cellular immunity and endometriosis. *Am J*
278 *Reprod Immunol* 1997;38:400-12
- 279 22. Lebovic DI, Bentzien F, Chao VA, et al. Induction of an angiogenic phenotype in
280 endometriotic stromal cell cultures by interleukin-1 β . *Mol Hum Reprod* 2000;6:269-75
- 281 23. Iwabe T, Harada T, Sakamoto Y, et al. Gonadotropin-releasing hormone agonist
282 treatment reduced serum interleukin-6 concentrations in patients with ovarian
283 endometriosis. *Fertil Steril* 2003;80:300-4
- 284 24. Matsuzaki S, Uehara T, Murakami J, et al. Quantitative analysis of estrogen
285 receptor alpha and beta messenger ribonucleic acid levels in normal endometrium and
286 ovarian endometriotic cysts using a real-time reverse transcription-polymerase chain
287 reaction assay. *Fertil Steril* 2000;74:753-59
- 288 25. Maitoko K, Sasaki H. Gonadotropin-releasing hormone agonist inhibits Estrone
289 sulfatase expression of cystic endometriosis in the ovary. *Fertil Steril* 2004;82:322-26
- 290 26. Vitale AM, Abramovich D, Peluffo MC, et al. Effect of gonadotropin-releasing
291 hormone agonist and antagonist on proliferation and apoptosis of human luteinized
292 granulosa cells. *Fertil Steril* 2006;85:1064-67

- 293 27. Ishihara H, Kitawaki JO, Kado N, et al. Gonadotropin-releasing hormone agonist
294 and danazol normalize aromatase cytochrome P450 expression in eutopic endometrium
295 from women with endometriosis, adenomyosis, or leiomyomas. *Fertil Steril* 2003;79:735-
296 42
- 297 28. Wang JH, Zhou FZ, Dong MY, et al. Prolonged gonadotropin-releasing hormone
298 agonist therapy reduced expression of nitric oxide synthase in the endometrium of women
299 with endometriosis and infertility. *Fertil Steril* 2006;85:1037-44
- 300 29. Belchetz PE, Plant TM, Nakai Y, et al. Hypophysial responses to continuous and
301 intermittent delivery of hypophthalamic gonadotropin-releasing hormone. *Science*
302 1978;202:631-33
- 303 30. Miller JD. Quantification of endometriosis-associated pain and quality of life during
304 the stimulatory phase of gonadotropin-releasing hormone agonist therapy: a double-blind,
305 randomized, placebo-controlled trial. *Am J Obstet Gynecol* 2000;182:1483-88
- 306 31. Gelety TJ, Pearlstone AC, Surrey ES. Short-term endocrine response to
307 gonadotropin-releasing hormone agonist initiated in the early follicular, midluteal, or late
308 luteal phase in normally cycling women. *Fertil Steril* 1995;64:1074-80
- 309 32. Meldrum DR, Wisot A, Hamilton F, et al. Timing of initiation and dose schedule of
310 leuprolide influence the time course of ovarian suppression. *Fertil Steril* 1988;50:400-2
- 311 33. Adamson GD, Kwei L, Edgren RA. Pain of endometriosis: effects of Nafarelin and
312 danazol therapy. *Int J Fertil Menopausal Stud* 1994;39:215-17
- 313 34. Fedele L, Bianchi S, Boccione L, et al. Buserelin acetate in the treatment of pelvic
314 pain associated with minimal and mild endometriosis: a controlled study. *Fertil Steril*
315 1993;59:516-21

- 316 35. Diugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot
317 suspension) in the treatment of endometriosis: a randomized, placebo-controlled, double-
318 blind study. *Lupron Study Group. Fertil Steril* 1990;54:419-27
- 319 35A. Rolland R, van der Heijden PFM. Nafarelin versus danazol in the treatment of
320 endometriosis. *Am J Obstet Gynecol* 1990;162:586-588
- 321 35b. Kennedy SH, Williams IA, Bodribb J et al. A comparison of Nafarelin acetate and
322 danazol in the treatment of endometriosis. *Fertil Steril* 1990;53:998
- 323 36. Bergquist A, Bergh T, Hogstrom L, et al. Effects of triptorelin versus placebo
324 controlled, double-blind study. *Lupron Study Group. Fertil Steril* 1998;69:702-708
- 325 37. Roux C, Pelissier C, Llistrat V, et al. Bone loss during GnRH agonist treatment and
326 use of nasal salmon calcitonin. *Osteoporosis Int* 1995;5:185-90
- 327 38. Moghissi KS, Schlaff WD, Olive DL, et al. Goserelin acetate (Zoladex) with and
328 without hormone replacement therapy for the treatment of endometriosis. *Fertil Steril*
329 1998;69:1056-62
- 330 39. Hornstein MD, Surrey ES, Weisberg GW, et al. Leuprolide acetate depot and
331 hormonal add-back in endometriosis: a 12 month study. *Lupron Add-back Study Group.*
332 *Obstet Gynecol* 1998;91:16-24
- 333 40. France HW, Van de Weiner PHM, Pennings TMM, et al. Gonadotropin-releasing
334 hormone agonist plus 'add-back' hormone replacement therapy for treatment of
335 endometriosis: a prospective randomized, placebo-controlled, double-blind trial. *Fertil*
336 *Steril* 2000;74:534-39

- 337 41. Riis BG, Christiansen C, Johansen JS, et al. Is it possible to prevent bone loss in
338 young women treated with luteinizing hormone-releasing agonists? *J Clin Endocrinol*
339 *Metab* 1990;70:920-24
- 340 42. Surrey ES, Gambone JC, Lu JK et al. The effects of combining norethindrone with
341 a gonadotropin-releasing hormone agonist in the treatment of symptomatic endometriosis.
342 *Fertil Steril* 1990;53:620-26
- 343 43. Agarwal SK. Impact of six months of GnRH agonist therapy for endometriosis. Is
344 there an age-related effect on bone mineral density? *J Reprod Med* 2002;47:530-34
- 345 44. Paoletti AM, Serra GG, Cagnacci A, et al. Spontaneous reversibility of bone loss
346 induced by gonadotropin-releasing hormone analog treatment. *Fertil Steril* 1996;65:707-10
- 347 45. Pierce SJ, Gazvani MR, Farquharson RG. Long-term use of gonadotropin-
348 releasing hormone analogs and hormone replacement therapy in the management of
349 endometriosis: a randomized trial with a 6 year follow-up. *Fertil Steril* 2000;74:964-68
- 350 46. Matsuo H. Prediction of the change in bone mineral density induced by
351 gonadotropin-releasing hormone agonist treatment for endometriosis. *Fertil Steril*
352 2004;81:149-53
- 353 47. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold
354 hypothesis. *Am J Obstet Gynecol* 1992;166:740-45
- 355 48. Fernandez H, Lucas C, Hédon B, et al. One year comparison between two add-
356 back therapies in patients treated with a GnRH agonist for symptomatic endometriosis: a
357 randomized double-blind trial. *Hum Reprod* 2004;19:1465-71

- 358 49. Surrey ES, Hornstein MD, for the Add-Back Study Group. Prolonged GnRH
359 agonist and add-back therapy for symptomatic endometriosis: Long-term follow-up.
360 *Obstet Gynecol* 2002;99:709-19
- 361 50. Delete – duplicate reference with 39
- 362 51. Surrey ES, Voigt B, Fournet N, et al. Prolonged gonadotropin-releasing hormone
363 agonist treatment of symptomatic endometriosis: the role of cyclic sodium etidronate and
364 low-dose norethindrone “add-back” therapy. *Fertil Steril* 1995;63:747-55
- 365 52. Mukherjee T, Barad D, Turk R, et al. A randomized, placebo-controlled study on the
366 effect of cyclic intermittent etidronate therapy on the bone mineral density changes
367 associated with six months of gonadotropin-releasing hormone agonist treatment. *Am J*
368 *Obstet Gynecol* 1996;175:105-9
- 369 53. Kiesel L, Schweppe KW, Sillem M, et al. Should add-back therapy for
370 endometriosis be deferred for optimal results? *Br J Obstet Gynecol* 1996;103:15-17
- 371 54. Surrey ES, Judd HL. Reduction of vasomotor symptoms and bone mineral density
372 loss with combined norethindrone and long-acting gonadotropin releasing hormone
373 agonist therapy of symptomatic endometriosis: a prospective randomized trial. *J Clin*
374 *Endocrinol Metab* 1992;75:558-63
- 375 55. Agarwal SK, Hamrang C, Henzl MR, et al. Nafarelin vs. leuprolide acetate depot
376 for endometriosis: changes in bone mineral density and vasomotor symptoms. Nafarelin
377 Study Group. *J Reprod Med* 1997;42:413-23
- 378 56. Bergquist A. A comparative study of the acceptability and effect of goserelin and
379 Nafarelin on endometriosis. *Gynecol Endocrinol* 2000;14:425-32

- 380 57. Nafarelin for endometriosis: a large-scale, danazol-controlled trial of efficacy and
381 safety, with 1 year follow-up: the Nafarelin European Endometriosis Trial Group (NEET).
382 *Fertil Steril* 1992;57:514-22
- 383 58. Shaw RW. Nafarelin in the treatment of pelvic pain caused by endometriosis. *Am J*
384 *Obstet Gynecol* 1990;162:574-76
- 385 59. Fedele L, Bianchi S, Arcaini L, et al. Buserelin versus danazol in the treatment of
386 endometriosis-associated infertility.. *Am J Obstet Gynecol* 1989;161:871-876
- 387 60. Shalev E. Gonadotropin releasing hormone and reproductive medicine. *J Obstet*
388 *Gynaecol Can* 2003;25:98-113
- 389 61. Rice VM. Conventional medical therapies for endometriosis. *Ann NY Acad Sci*
390 2002;955:343-52
- 391 62. Küpker W, Felberbaum RE, Krapp M, et al. Use of GnRH antagonists in the
392 treatment of endometriosis. *Reproductive BioMedicine On Line* 2002;5:12-16
- 393 63. Donnez J, Peresada O, Barukov a. Dose-finding study of the LHRH antagonist
394 cetorelix, given over a period of 8 weeks, in the treatment of endometriosis. Evidence
395 Based Obstet Gynecol 2004;6:00:00
- 396 64. Morimoto C, Osuga Y, Yano T, et al. GnRH II as a possible cytostatic regulator in
397 the development of endometriosis. *Hum Reprod* 2005;20:3212-218
- 398 65. Hornstein MD, Hemmings R, Yuzpe AA, et al. Use of Nafarelin versus placebo
399 after reductive laparoscopic surgery for endometriosis. *Fertil Steril* 1997;68:860-64
- 400 66. Vercellini P, Crosignani PG, Fadini R, et al. A gonadotrophin releasing hormone
401 agonist compared with expectant management after conservative surgery for symptomatic
402 endometriosis. *Br J Obstet Gynaecol* 1999;106:672-79

403 **Table I. Side Effects of GnRH Agonists**

- 404 • Hot flashes (80%-90%)
- 405 • Sleep disturbances (60%-90%)
- 406 • (30%) Vaginal dryness
- 407 • Joint pain (30%)
- 408 • Breakthrough bleeding (20%-30%)
- 409 • Headaches (20%-30%)
- 410 • Mood change (10%)
- 411 • Bone loss (↓ bone density 5%-6%)
- 412 • Adverse lipid changes (↑ LDL, ↓ HDL)

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

414

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