Long-term Gonadotropin-releasing Hormone Agonist Therapy: The Evolving Issue of Steroidal “Add-back” Paradigms

Eli Y Adashi

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, The University of Maryland School of Medicine, Baltimore, MD, USA

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Abstract. The introduction of steroid “add-back” regimen draws on the recognition that several clinical entities targeted for treatment with GnRHa are not “six-month diseases”. Included under this heading are individuals suffering from symptomatic endometriosis (not desirous of pregnancy), uterine fibroids (ineligible or disinterested in definitive surgical therapy), ovarian hyperandrogenism, premenstrual syndrome, menopausal transition, or dysfunctional uterine bleeding. A six month course of therapy with a GnRHa does not adversely affect lipoprotein economy and therefore presumably the corresponding cardiovascular risk. A six month course of GnRHa therapy appears to be associated with a substantial decrease (of up to 8.2%) in lumbar bone density, a phenomenon which may not be entirely reversible six months after discontinuation of therapy. In principle, steroid “add-back” therapy should diminish some or all of the side effects associated with GnRHa therapy, may provide a medical treatment option for patients representing a high surgical risk, and may delay surgical intervention if desired. On the other hand, a steroid “add-back” therapy may delay tissue diagnosis, be associated with a substantial cost as well as with the need in parenteral route of administration. Norethindrone-only (but not medroxyprogesterone acetate-only) “add-back” regimens have proved promising in the context of endometriosis. Non-concurrent estrogen/progestin “add-back” regimens proved promising in the context of uterine fibroids. Substantial additional studies would have to be carried out to validate the utility of steroid “add-back” regimens. Special emphasis will have to be placed on the evaluation of long-term utility with an eye towards assessing clinical efficacy, impact on lipoprotein economy, impact on bone density, impact on urogenital tissues, and impact on the hot flash. The concurrent or non-concurrent use of non-steroid “add-back” regimen will also most likely constitute a major component of future studies. (Keio J Med 44 (4): 124-132, December 1995)

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Introduction

There is little doubt that the introduction of Gonadotropin-Releasing Hormone Agonists (GnRHa) has all but revolutionized the practice of Reproductive Endocrinology.1-9 In this connection, special mention must be made of the highly successful short-term (up to 4 weeks) application of these principles in the context of Assisted Reproductive Technology.10 Equally important however is the application of GnRHa under circumstances calling for their longer-term application. In this connection, special consideration must be given to the already established salutary effects of these principles when applied for up to six months to the management of endometriosis,11-37 uterine fibroids,38-62 or precocious puberty.63-67 It is in these contexts that the unique ability of GnRHa to put the reproductive axis at rest, at will, for the duration of the therapy is being put to good use.

The above notwithstanding, current therapeutic regimens involving the use of GnRHa must be viewed as restrictive in terms of the permissible duration of application. Indeed, with the exception of the indication of precocious puberty, use of GnRHa in the context of
reproductive endocrine disorders (e.g. endometriosis or uterine fibroids) is limited to 6 months in duration. Understandably, this latter cap was prompted by concerns relevant to the possibility that longer-term application of GnRHa may result in profound and potentially irreversible bone loss not to mention other consequences of the hypoestrogenic state which inevitably ensues. Fortunately for subjects afflicted with endometriosis-associated infertility, a six-month therapeutic regimen may (at times) be all that is required for the genesis of a temporary yet indispensable fertile time window. Not so however is the case for subjects presenting with symptomatic endometriosis whose concerns are of a longer-term nature and whose management may require an opened-ended approach. Similar considerations apply to select subjects afflicted with symptomatic uterine fibroids for whom a surgical option must be ruled out. Clearly then, specific therapeutic needs raised by day to day clinical practice requirements may not be satisfactorily met by current therapeutic strategies. If nothing else, it is this line of reasoning which recognizes the fact that many of the disease states targeted for treatment with GnRHa are not "six-month diseases". Indeed, should GnRHa be applied in the context of chronic afflictions such as ovarian hyperandrogenism, the menopausal transition, or the premenstrual syndrome, longer-term application strategies would inevitably have to be devised. Undoubtedly, the long-term provision of GnRHa by itself would constitute an unreasonable therapeutic proposition, given the inevitable consequences of the long-term hypoestrogenic state. It is precisely this therapeutic challenge which underlies the rationale for steroid "add-back" therapy to which this review is dedicated.

On the surface at least, chronic applications of GnRHa could have been made possible by adjunctive estrogen replacement therapy. However, as intuitive reasoning would clearly indicate, such therapeutic maneuver could (in the context of estrogen-dependent pathology) run the risk of undermining the very purpose of the treatment designed to achieve the therapeutic hypoestrogenic state required. Exceptions to this line of reasoning may include several therapeutic indications such as the example of ovarian hyperandrogenism, an androgen- rather than an estrogen-dependent state wherein no apriori contraindication exists for sex steroid replacement. On the contrary, the concurrent provision of estrogen/progestin replacement therapy may well prove of therapeutic benefit in this context. In most other circumstances however, careful evaluation must be undertaken of the feasibility and utility of "steroid add-back" in the context of estrogen-dependent disease states.

It is the purpose of this communication to critically review the current status of GnRHa/steroid "add-back" regimens in an effort to assess the prospects of such therapeutic strategy. Admittedly, efforts along these lines may well be viewed as naive and as attempting to "have one's cake and eat it too". However, serious consideration must be given to the prospect that adjunctive steroid replacement therapy could be safely provided against the backdrop of long-term GnRHa application in the best interest of those clinical conditions currently beyond the reach of contemporary GnRHa therapy.

Why Steroid “Add-back” Therapy?

As might be expected, the response to the above query would appear self-evident. Indeed, the question might well be viewed as rhetoric in that the rationale for steroid "add-back" therapy in the context of long-term GnRHa application would inevitably be to combat the consequences of the GnRHa-induced hypoestrogenic state. In this connection, a series of well-defined consequences, not unlike those experienced in the climacteric would have to be addressed. For example, issues of quality of life, ie the occurrence of urogenital atrophy and of hot flashes are clearly in need of effective redress. More importantly however, consideration must be given to the attenuation and possibly virtual elimination of the more serious (and potentially life-threatening) consequences of the hypoestrogenic state, ie increased bone loss and decreased cardioprotection. Indeed, it is these latter complications which affect the quantity rather than the quality of life.

In attempting to define the issues at hand, the key question which must be answered has to do with the feasibility of the design of "add-back" regimens which would allow the long-term application of GnRHa. Moreover, efforts must be directed at establishing whether it is possible to diminish the adverse side effects associated with GnRHa therapy without compromising therapeutic efficacy.

GnRHa-induced Cardiovascular Risks

Despite the central importance of cardiovascular parameters to long-term GnRHa application, relatively little information is available to address this issue at this time. Indeed, heavy reliance must be made on studies wherein GnRH agonists were applied for a total of 6 months in keeping with current guidelines.\textsuperscript{25,26,68-75} Unfortunately, even that data base proves relatively limited, the overall literature experienced thus far totaling 479 subjects. Inevitably, no information is available at this time with respect to actual GnRHa-associated cardiovascular events. Rather, heavy use is being made of the predictive value of the circulating lipoprotein pattern. Given this parameter, the literature appears highly uniform in documenting the fact that the provision of GnRHa for a total of 6 months is without a measurable adverse effect on the lipoprotein pattern as assessed in
terms of the circulating levels of LDL and HDL. Indeed, whereas the circulating levels of LDL proved invariably unchanged [with one exception\(^7\)], the circulating levels of HDL were judged to be stable\(^7\) or increased.\(^25,26,69,71\) As such, these findings would suggest a short-term (6 month) lipid-neutral effect of GnRHa with a possible slight net gain as gauged by the circulating levels of HDL.

It goes without saying that the preceding observations provide relatively little insight as it concerns the longer-term application of GnRHa. However, common sense alone would dictate that the induction of a long-term hypoestrogenic state would in fact result in progressively diminishing cardioprotection as has previously been documented for the menopause.\(^76,77\) That notwithstanding, it is not inconceivable that the profound differences between naturally-occurring menopause and its GnRHa-induced counterpart may in fact produce outcomes not immediately predicted by conventional wisdom drawing on experience from the climacteric hyperestrogenic state. Moreover, given that steroid “add-back” therapy will undoubtedly be required in the context of long-term GnRHa application, it would appear prudent to hold judgement on this all important issue until such time that prospective, controlled, double-blind studies have been completed. Intuitive reasoning alone would suggest that the beneficial effects accrued from the post-menopausal provision of sex steroid therapy may well apply in the context of GnRHa-induced hypoestrogenism.

**GnRHa-induced Bone Loss**

Despite intense concerns as to the possibility of GnRHa-induced bone loss,\(^78-80\) relatively little is offered by the literature in this regard. Indeed, thorough evaluation of the world’s English-speaking medical literature yields interpretable information on less than 900 subjects.\(^74,75,81-101\) The largest series of patients studied involved a total of 315 individuals.\(^37\) Moreover, the very first relevant reports on this important issue dates back only to 1987.\(^82,83\) Consequently, despite the fact that GnRHa are being used world-wide by a very substantial number of women, the impact of such therapy on short-term bone loss remains relatively poorly documented. In fact, the information available proves conflicting and puzzling thereby clearly emphasizing a real need in the execution of large controlled studies in this connection.

The studies available, involving for the most part subjects afflicted with endometriosis or uterine fibroids, made use of different brands of GnRHa applied at variable dose ranges and via different routes. Consequently, it is reasonable to assume that the overall therapeutic efficacy of the regimens in question varied highly particularly with regards to the intensity of the hypoestrogenic state which may have been induced. Indeed, it is this very line of reasoning which may well provide the most plausible explanation for the otherwise remarkable disparity documented between individual therapeutic regimens.

In some, but not all cases, specific information is available as to the impact of a six-month treatment with a GnRHa on bone density as assessed at the level of the lumbar spine and the distal radial bone.\(^49,52,74,75,83-86,88,90-96,98-102\) The former, representative largely of alterations in trabecular bone economy, was variably assessed by double photon absorptiometry, quantitative computed tomography, and even DEXA technology. Unexpectedly, a wide range of quantitative alterations was noted. Specifically, little or no change in lumbar bone density proved the case in some studies.\(^86,88,96\) In contrast, losses of up to 8.2% were noted in similarly-studied patient populations.\(^98\) Moreover, 5.7% and 4.9% decreases were noted using precise DEXA technology.\(^74,100\) As such, these observations are compatible with the view that the impact of a six-month course of a GnRHa on lumbar bone density is highly variable. In principle, it is difficult to conceptualize an 8.2% bone loss at the level of the lumbar spine occurring within a total of 6 months given that the worse case scenario in context of the climacteric generally does not exceed 3%/year.\(^103\) A similarly-heterogenous body of information is available for measurements, carried out at the level of the distal radius. Although the reason(s) underlying the high degree of variability and apparent severity of some of the preceding observations remain unknown, serious consideration must be given to the possibility that some of the differences in question may be attributable to the methods of measurement, their level of reproducibility, the involvement of distinct patient populations, and the employment of highly distinct therapeutic regimens.

Wherever available, limited albeit relatively uniform published information is in keeping with the possibility that the actions of GnRHa at the level of bone involve an overall increase in bone turnover parameters.\(^73,81,82,84,87,94,96,98\) Specifically, note was made of GnRHa-induced increments in parameters reflecting both bone formation (serum osteocalcin and alkaline phosphatase) and bone resorption (serum phosphorous and the creatinine-normalized urinary excretion of hydroxyproline and calcium). Although the precise mechanism(s) whereby GnRHa therapy may promote bone turnover remain uncertain, there is little doubt but that the new steady state is due, if only in part, to the hypoestrogenic state so induced. Given that the net effect of GnRHa therapy is a decrease in overall bone mineral density, it is highly likely that the GnRHa-induced increase in bone turnover is unbalanced in nature. Specifically, it is highly likely that enhancement of bone resorption exceeds the apparent attendant increase in bone formation.

Yet another critical facet relevant to the impact of
GnRHa on bone economy concerns the reversibility of GnRHa-induced bone loss. Indeed, the very premise for the six-month treatment cap is the presumption that whatever bone loss may accrue in the course of the therapy would prove reversible upon discontinuation of the same. Although the literature offers relatively limited insight into this key issue, several, but by no means all reports are in keeping with the observation that discontinuation of treatment will be associated with a virtually complete recovery of bone loss when evaluated 6 months following discontinuation of therapy. Indeed, a small but persistent body of literature appears to suggest that the GnRHa-induced bone loss may not be entirely reversible and may in fact be characterized by a net decrease in bone density of up to 5.4% when assessed 6 months after discontinuation of therapy. A recent report employing precise DEXA technology suggested incomplete recovery at 6 months the residual bone loss being 4.2%.\(^7\) All told, the current literature suggests that treatment with GnRHa for 6 months may be associated with a significant and not necessarily reversible decrease in bone mineral density, an effect due to enhanced (presumably unbalanced) bone turnover. Besides highlighting the need in additional studies, these observations strongly suggest that steroid “add-back” is likely to prove indispensable to bone health in the context of long-term (and quite possibly short-term) GnRHa application.

Objectives, Advantages, and Disadvantages of Steroid “Add-back” Therapy

As might be anticipated from the complex of symptoms characterizing the GnRHa-induced hypoestrogenic state, the objectives of steroid “add-back” therapy would be to provide cardioprotection as well as prevent bone loss, hot flashes, and urogenital atrophy. In this respect, “steroid add-back” therapy is not unlike standard hormone replacement therapy as applied in the context of the menopausal state.

Although the potential advantages of “add-back” therapy would appear self-evident, the following listing of benefits appears worthy of further emphasis: 1) Diminution of some or all of the side effects associated with GnRHa therapy. 2) Provision of a medical treatment option to patients representing a high surgical risk. Accordingly, patients in whom surgical intervention is contra-indicated for medical reasons may benefit from long-term therapy, an option previously receiving relatively limited attention. 3) Delaying (virtually indefinitely) surgical intervention if desired. Indeed, “add-back” therapy has the potential of providing flexibility not possible with a limited (6 months) course of therapy as regards the surgical scheduling of anticipated or inevitable surgical procedure. The above notwithstanding, steroid “add-back” therapy is not without its relative shortcomings: 1) Long-term steroid “add-back” therapy may delay tissue diagnosis in that the surgical intervention is either bypassed or postponed. Indeed it is not conceivable that under such circumstances, the diagnosis of prognostically-poor entities such as uterine sarcoma may be missed or overlooked. Although the incidence of such occurrence is likely to be relatively limited, precedents already exist. The reason why such a condition is likely to be rare has to do with the fact that the overall incidence of uterine sarcoma is 1.7/100,000 women age 20 years or more. 2) It goes without saying that provision of steroid “add-back” therapy at this time will be associated with increased cost reflecting largely the GnRHa component. What’s more, given that steroid “add-back” therapy is not FDA-approved at this time as a therapeutic strategy, no reimbursement can at this time be anticipated from third party payers. 3) Given the absence of an orally-administered GnRHa, current long-term GnRHa/steroid “add-back” therapy would require a parenteral route of GnRHa administration (IM, SC, IN).

Clinical Indications for GnRHa/steroid “Add-back” Regimens

Given the relatively short history of the very concept of GnRHa/steroid “add-back” therapy, the indications for such an approach are still in a stage of evolution. Although preliminary, the following list constitutes an example of promising clinical entities to be targeted.

Symptomatic endometriosis in individuals not desirous of pregnancy

In this case, the individuals most likely to benefit from a GnRHa/steroid “add-back” regimen are those in whom GnRHa therapy for symptomatic endometriosis has to be prematurely discontinued following a six-month course. Given that the “grace” period to follow is likely to be limited, the individuals in question invariably request continued relief. Unfortunately, repeated courses of GnRHa therapy, although feasible, have not been approved as such and do not at this time constitute the standard of care for fear of substantial, cumulative bone loss. Consequently, if one were to wish to provide continued sustained relief, long-term GnRHa administration with steroid “add-back” protection would prove highly desirable. It is equally likely that incidentally-discovered endometriosis (for example in the course of an appendectomy) could benefit from long-term prophylaxis by way of a GnRHa/steroid “add-back” regimen. Clearly, no such option exists at this time thereby dooming the patients in question to progressive aggravation of the endometriotic state to a point where it may become symptomatic and/or causally-related to future infertility.
Symptomatic uterine fibroids in individuals who are either ineligible or do not wish definitive surgical therapy

Falling under this heading are a large number of patients in their early 40’s who could in principle be carried on a medical regimen into the menopause at which point the very issue of the uterine fibroid may become non-applicable.

Ovarian hyperandrogenism

Reserved primarily for individuals with moderate to severe ovarian hyperandro-genism, long-term GnRHa/steroid “add-back” therapy has been practiced for some time. Clearly, this clinical circumstance is unique in that there is no apriori contraindication for the use of steroid “add-back” therapy. Indeed, the very purpose of the therapy is only to lower the circulating levels of androgens. In this case, the replacement of sex steroids does not in any way undermine the purpose of the therapy and as such is perfectly compatible with the therapeutic objectives. Considering that GnRHa constitutes the most potent means available to date for the suppression of the reproductive axis, the long-term use of these principles could clearly benefit individuals severely affected by this chronic condition.

Premenstrual syndrome

Although the precise etiology of the premenstrual syndrome remains a matter of study, efforts directed at interrupting the cyclic nature of this clinical entity have proved of some value. This issue has been most directly addressed by Mortola and Associates whose study clearly revealed that the long-term application of a GnRHa together with steroid “add-back” therapy could prove useful in the context of the premenstrual syndrome. Here again, the clinical condition is uniquely suited for steroid “add-back” therapy in light of the fact that sex steroid replacement may be perfectly compatible with the objectives of therapy.

In a double-blind placebo-controlled study, 60 women age 21-45 years were randomized to one of three treatment groups: placebo implant every 4 weeks plus placebo estrogen replacement therapy tablets daily, goserelin (3.6 mg) implants every 4 weeks plus placebo estrogen replacement therapy tablets daily, or goserelin (3.6 mg) implants every 4 weeks plus estradiol valerate (2 mg/day) with norethindrone (5 mg from days 22-28). DEXA scans were performed before treatment and again after 6 treatment cycles. Note was made of the fact that the estrogen/progestin “add-back” therapy prevented any change in bone density as compared with either pretreatment values or the group receiving placebo plus placebo. The study must be qualified by the recognition of a drop out rate of 32%. All told, this study suggests, if nothing else, the ability of the estrogen/progestin regimen to protect women from bone loss at the level of the lumbar spine and femoral neck for the 6 months of the therapy.

Menopausal transition

Although relatively limited attention has been paid to the menopausal transition as a distinct clinical entity, such recognition appears long overdue. This component of the reproductive life cycle is commonly and unfortunately afflicted by a series of complications for which no specific uniformly effective therapy is currently available. “Easing” women into the menopause by way of combination oral contraceptive – or GnRH-induced suppression of reproductive function until the actual menopause sets in could prove to be a useful strategy. For the latter, no obvious contraindication would exist for the replacement of sex steroids in that the artificial induction of a reversible menopause-like state virtually clearly some form of sex steroid replacement.

Dysfunctional uterine bleeding

This often debilitating clinical circumstance has proven difficult to manage. In an effort to provide an improved therapeutic option, several investigators examined the possibility of utilizing a long-term therapeutic approach with GnRHa combined with steroid “add-back” therapy. In one such case, use was made of subcutaneously administered leuprolide at the 1 mg/day dose level. This in turn was supplemented with transdermal estrogen therapy 50 µg/day twice weekly followed by the sequential administration of MPA at the 10 mg/day dose level between days 21-28 of each cycle. This approach resulted in regular withdrawal bleeding of normal volume and stabilized the hematologic parameters for the duration of the therapy.

Similarly, Thomas and Associates carried out an open observational study comparing menstrual blood loss before, during and after 3 months of treatment with a combination of a long-acting GnRHa and cyclic hormone replacement therapy. A total of 20 women complaining of heavy menstrual loss participated in the study. The drugs employed included depot goserelin along with cyclic hormone replacement therapy (1 mg of cyclopregynova). Although quantitative assessment was subject to obvious limitations, the evidence suggested a decrease in overall menstrual loss.

More recently, Vercellini et al reported on the case histories of 23 subjects whose chronic anovulatory bleeding pattern (associated with severe iron-deficiency) was managed for 6 months with Depo-Goserelin. Monitored before and after this course of therapy, the patients...
in question displayed an increase in the circulating levels of hemoglobin from 7.9 to 13.8 gm/dL, comparable increments being noted for the hematocrit (from 26 to 41.6%), the serum iron (from 19.8 to 63.3 μg/dL), and serum ferritin (from 6.2 to 35.3 ng/mL). The endometrial hyperplasia observed in 11 subjects displayed regression at the time of a follow-up suction biopsy. These observations support the utility of GnRHa in the context of acute severe dysfunctional uterine bleeding associated with iron-deficiency anemia. Clearly, this form of therapy cannot be expected to rectify the underlying anovulatory disorder; however, a short-term treatment course might indeed allow for hematologic recovery and hence a more leisurely discussion of long-term disposition.

**Breast cancer prevention**

To preliminarily address the possibility of preventing breast cancer with a long-term regimen of GnRHa along with steroid “add-back” therapy. Spicer and associates have examined a prototype contraceptive consisting of a depot Lupron preparation administered intramuscularly (7.5 mg) every 28 days complemented with low doses of an oral estrogen (0.625 mg of conjugated estrogen for 6 days every week) and intermittent oral progesterone (10 mg of medroxyprogesterone acetate for 13 days every 4 months). Eighteen subjects previously shown to display a 5-fold or greater increased breast cancer risk were involved and randomized as follows: Twelve of the patients were assigned to the contraceptive arm whereas 6 of the patients were assigned to the control arm. For the most part, scheduled vaginal bleeding was observed. More importantly, a beneficial rise was noted in the circulating levels of HDL cholesterol in the treatment group. However, despite the employment of an estrogen dose known to protect postmenopausal women from bone loss, a total annual loss of 1.9% was detected in the treatment group. Conceivably, the latter decrease may have represented inhibition of ovarian androgen production by the GnRHa. This preliminary study is anticipated to prove a forerunner for additional studies in this area before too long.

**References**

5. Andreyko JL, Marshall LA, Dumesc DA, Jaffe RB: Thera-


60. Adamson GD: Treatment of uterine fibroids: current findings
88. van Leudsen HA, Dogterom AA: Rapid reduction of uterine leiomyomas with monthly injections of D-Trp6-GnRH. Gynecol Endocrinol 1988, 2: 45–51
90. Dawood MY, Lewis V, Jortctal and trabecular bone mineral content in women with endometriosis: effect of gonado-
95. Whitehouse RW, Adams JE, Bancroft K, Vaughan-Williams


