Review Article

Gonadotropin releasing hormone agonists: Expanding vistas

Navneet Magon

Department of Obstetrics and Gynecology, Air Force Hospital, Kanpur, India

ABSTRACT

Gonadotropin-releasing hormone (GnRH) agonists are derived from native GnRH by amino acid substitution which yields the agonist resistant to degradation and increases its half-life. The hypogonadotropic hypogonadal state produced by GnRH agonists has been often dubbed as "pseudomenopause" or "medical oophorectomy," which are both misnomers. GnRH analogues (GnRH-a) work by temporarily "switching off" the ovaries. Ovaries can be "switched off" for the therapy and therapeutic trial of many conditions which include but are not limited to subfertility, endometriosis, adenomyosis, uterine leiomyomas, precocious puberty, premenstrual dysphoric disorder, chronic pelvic pain, or the prevention of menstrual bleeding in special clinical situations. Rapidly expanding vistas of usage of GnRH agonists encompass use in sex reassignment of male to female transsexuals, management of final height in cases of congenital adrenal hyperplasia, and preserving ovarian function in women undergoing cytotoxic chemotherapy. Hypogonadic side effects caused by the use of GnRH agonists can be tackled with use of "add-back" therapy. Goserelin, leuprolide, and nafarelin are commonly used in clinical practice. GnRH-a have provided us a powerful therapeutic approach to the treatment of numerous conditions in reproductive medicine. Recent synthesis of GnRH antagonists with a better tolerability profile may open new avenues for both research and clinical applications. All stakeholders who are partners in women's healthcare need to join hands to spread awareness so that these drugs can be used to realize their full potential.

Key words: Add-back, endometriosis, GnRH, gonadotropin-releasing hormone agonists, goserelin, infertility, leuprolide, zoladex

Introduction

Just around two centuries ago, distinguished gynecologists and psychiatrists supported the practice of ovariotomy—the surgical removal of normal ovaries, for the treatment of "menstrual madness." "Menstrual madness" of 19th century equates with today's premenstrual dysphoric disorder (PMDD). The procedure was first performed in 1872 and was referred to as "Battey's Operation" in the USA after Robert Battey of Georgia and by the name of "Tait's Operation" in Britan after Lawson Tait of Birmingham. Incidentally, the same surgery was performed in nymphomaniacs, patients with neurasthenia, "hysterical vomiting," epilepsy, and dysmenorrhea, and to "cure" masturbation. Since the then surgeons had no idea of menopausal symptoms or osteoporosis, they would perform this operation without guilt and without anticipating the severe medical problems that often ensued, but since it would cure the women's cyclical monthly symptoms, it was gratifying. So, limited was the understanding of the menstrual cycle in that era that amenorrhea following ovariotomy came as a surprise! However, this surgical procedure was advancement in treatment, because before the advent of such operations, the common practice among physicians was to apply leeches to the lower abdomen, vulva, and anus to alleviate premenstrual symptoms. It was later realized that the secretions of ovary are controlled by the secretions from pituitary, which in turn is controlled by hypothalamus through its own secretions. With the elucidation of the last mentioned secretions in the form of

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.85575

Corresponding Author: Dr. Navneet Magon, Obstetrician, Gynecologist and Endoscopic Surgeon, Department of Obstetrics and Gynecology, Air Force Hospital, Kanpur, India. E-mail: navneetmagon@gmail.com

the structure of Gonadotropin-releasing hormone (GnRH) by Guillemin and Schally in 1967, it became possible to synthesize thousands of different analogues of the primary decapeptide, GnRH. Agonists were recognized early on and have been employed in clinical medicine for more than 25 years. The way research in this area of medicine is moving, there is almost no subspecialty of medicine that will be left untouched by the GnRH and its analogues. Medicine has travelled a long way, wherein PMDD is no more thought of as "menstrual madness," whereas performing an ovariotomy for PMDD may be thought of an "act of madness!"

What are Gonadotropin-Releasing Hormone Agonists?

GnRH agonists are derived from native GnRH by substitution of a D-amino acid for the native L-amino acid at position 6 in the decapeptide. GnRH has a short half-life because of the rapid cleavage of the bonds between amino acids at positions 5–6, 6–7, and 9–10. Substitution at position 6 yields the agonist resistant to degradation and increases it's half-life and the time of receptor occupancy. Follicle-stimulating hormone and luteinizing hormone (LH) secretion from the pituitary requires a pulsatile secretion of GnRH from hypothalamic, which allows receptor concentrations to be replenished between pulses. A constant intravenous infusion of GnRH or administration (subcutaneous/intramuscular/intranasal) of GnRH agonists (goserelin, leuprolide, nafarelin, buserelin, triptorelin) causes an initial agonistic action or the *"flare"* response, followed by downregulation of receptor concentrations, which desensitizes the pituitary to continued stimulation. The *"flare"* response is because of the release of the gonadotropins which are already produced and stored in pituitary, and indeed "flare" is greatest in the early follicular phase when GnRH and estradiol have combined to create a large reserve pool of gonadotropins. Within 3 to 4 weeks, it induces a hypogonadotropic - hypogonadal state, a situation simulating WHO Group-1 anovulation (hypogonadotropic hypogonadal anovulation).[1] Initially, this response is due to desensitization and downregulation and the same is sustained because of gradual loss of receptors and the uncoupling of the receptor from its effector system. In addition, postreceptor mechanisms lead to secretion of biologically inactive gonadotropins, which may still be detected by immunoassay. It is also not out of place to mention here that GnRH antagonists, which are synthesized with multiple amino acid substitutions, act by binding to the GnRH receptors and provide competitive inhibition of the naturally occurring GnRH. Consequently, they produce an immediate decline in gonadotropin levels and provide a therapeutic effect within 24 to 72 hours. The early products either lacked potency or were associated with undesirable side effects due to histamine release; however, new products are now available which are potent and have no use-prohibiting side effects. GnRH agonists and antagonists collectively form the class of drugs called GnRH analogues (GnRH-a).

The hypogonadotropic hypogonadal state produced by GnRH agonists has been often dubbed as "pseudomenopause" or "medical oophorectomy."[2,3] Both these terms are, however, misnomers. Because, in menopause, the ovaries stop producing estrogen because they are depleted of follicles and in oophorectomized women, the ovaries are altogether absent, question of them secreting anything does not arise. In both these cases, serum gonadotropin levels are elevated. In contrast, women under treatment with GnRH agonists do not produce estrogen because their ovaries do not receive gonadotropin stimulation and gonadotropin levels are very low. So, the parlances like GnRH agonist treatments do bring a "pseudomenopause" or giving GnRH agonists that is like performing a "medical oophorectomy" are scientifically incorrect and should not be used.

The GnRH-a cannot escape destruction if administered orally. Higher doses administered subcutaneously achieve almost equal effect as observed with intravenous and intramuscular treatment; however, the smaller blood peaks are slower to develop and take longer to return to baseline. Other forms of administration include nasal spray, sustained-release implants, and injections of biodegradable microspheres. The route may vary for the specific drug. Approximately 75% of women are rendered hypogonadal within 4 weeks of treatment and almost all are rendered so by 8 weeks.[4,5]

What is Undesirable About Gonadotropin-Releasing Hormone Agonists?

The major side effects of GnRH agonists are those of hypogonadism and include hot flashes, decreased libido (especially because androgen production is also suppressed along with estrogen), breakthrough bleeding, vaginal dryness, irritability, fatigue, headache, depression, changes in skin texture, and bone mineral depletion. The most common symptom reported is vasomotor symptom which troubles more than 80% women put on GnRH agonist therapy and almost 30% do report vaginal symptoms and headache. However, what concerns most is the decrease in bone mineral density. Standard GnRH agonist treatment

regimens of 6 months cause significant bone loss in both the trabecular and cortical bone which manifests typically at lumbar spine and femoral neck, respectively. The bone loss may even exceed 1% per month.[6-8] Once the treatment is discontinued, bone loss recovers slowly, but may not be completely recovered in all women.[8-12]

"Add-Back" with a Desire to Prevent the Undesirable

To prevent the bone mineral depletion that accompanies GnRH agonist therapy, a number of different "add-back" treatment strategies have been developed. Commonly employed "add back" regimens are as follows: low-dose combined estrogen-progestin;[13,14] estrogen-only, which however is not very advisable;[15] progestins alone; bisphosphonates;[16] tibolone;[7] and selective estrogen receptor modulator, raloxifene.[17] Combined estrogen-progestin add-back treatment regimens protect bone and have the added advantage of preventing hot flushes and the development of genitourinary atrophy. Add-back therapy must be started simultaneously with the start of GnRH agonist.[18] However, adolescents with symptomatic endometriosis who might be required to be treated with these drugs present a unique challenge, because these young women have not yet achieved peak bone mass. A recent retrospective review of 36 adolescent girls by Di Vasta *et al*.[19] has shown that add-back is effective in providing symptom relief and bone health in the majority of adolescents, still the author strongly advocates monitoring of bone mineral density in this subset of patients. This is one area where more evidence is desirable.

Uses of Gonadotropin-Releasing Hormone Analogues: Expanding Vistas

GnRH-a work by "switching off" the ovaries, albeit, temporarily. Ovaries can be "switched off" for the treatment of endometriosis, adenomyosis, uterine leiomyomas, precocious puberty, PMDD, chronic pelvic pain, or the prevention of menstrual bleeding in special clinical situations (e.g., in thrombocytopenic patients).

Subfertility

GnRH-a have opened new vistas in the management of female subfertility. The introduction of long-acting GnRH agonists in the late 1980s revolutionized the approach to ovarian stimulation in assisted reproductive technologies (ART) by providing the means to suppress endogenous pituitary gonadotropin secretion and thereby prevent a premature LH surge during exogenous gonadotropin stimulation. Combination therapy with GnRH agonists and gonadotropins, also called "superovulation therapy," has been advocated and extensively investigated for ovarian stimulation in *in vitro fertilization*.[20-22] This has been particularly effective in women who respond poorly to gonadotropin stimulation or who have premature ovulation and has resulted in an increase in pregnancy rate. Pulsatile administration of GnRH in physiologic amounts at a frequency that mimics endogenous release stimulates the ovaries. This has been used to induce ovulation in anovulatory conditions, such as hypothalamic amenorrhea and polycystic ovarian disease.[23,24]

Endometriosis

One area where GnRH agonists have brought wonders is treatment of endometriosis. They have been proven effective in relieving pain in women with endometriosis. GnRH agonists are effective for the treatment of endometriosis because they induce a hypogonadal state, which deprives existing disease of estrogen support, and amenorrhea, which prevents new peritoneal seedlings. However, once the treatment is stopped, pain of lesser or equal intensity may recur and the recurrence rate is at around 10 to 20% per year.[25-27] The overall cumulative recurrence rate 5 years after treatment with a GnRH agonist is approximately 55%; it is around 37% for women with minimal and mild endometriosis but double the rate, i.e., 74%, for those with advanced disease.[28] Treatment with GnRH agonists can many a times decrease the size of endometriomas, although it might not be able to eliminate them.[29] All GnRH agonists have been found to have similar suppressive effects on endometriosis. As far as fertility is concerned, pregnancy rates in subfertile women receiving GnRH agonist therapy for subfertility associated with endometriosis is similar to that in women treated with danazol or progestational agents. Ovulatory cycles usually return to normal within 1 to 3 cycles after cessation of GnRH agonist treatment.

Precocious puberty

"Switching off" the ovaries can delay puberty in individuals with precocious puberty. Maturation of the pituitary-gonadal system requires pulsatile GnRH stimulation. Idiopathic precocious puberty can be viewed as a disorder characterized by premature hypothalamic GnRH activity. Suppression of pituitary-gonadal function has been the aim of various therapeutic methods. Long-term administration of GnRH agonists has proven to be remarkably safe and effective for precocious puberty.[30,31] Within 6 to 18 months after beginning treatment with an agonist, pubertal levels and patterns of secretion of gonadotropins and sex steroids revert to prepubertal levels and patterns. A more striking aspect of this therapy is the regression of

secondary sexual characteristics and cessation of menstrual bleeding. The effects of therapy usually reverse when treatment is discontinued, gonadotropin and sex steroid secretion resume, and the child follows the expected clinical progression through normal puberty.

Fibroids

Uterine leiomyomas, or fibroids as they are more commonly called, are the most common benign tumors of the female reproductive tract. It has long been recognized that estrogens may stimulate the growth of leiomyomata, which has been supported by the observation of these tumors regressing in hypoestrogenic states as in menopause. GnRH agonists, because of their ability to create profound hypoestrogenism, have been used for medical treatment of leiomyomata. The use of GnRH agonists in the treatment of leiomyomata may obviate the need for surgery in a few cases or at least decrease the surgical risk by diminished size of remaining fibroid tissue. It has been shown that treatment with GnRH agonist for a 3-month duration results in a 40% to 60% decrease in the mean uterine volume.[32-34] The maximum reduction in uterine volume is usually noted by the third month of treatment. Uterine volume may return to the pretreatment size within next 6 months. Thus, the main goals of preoperative treatment with GnRH agonists are to reduce blood loss during subsequent hysterectomy or myomectomy. One more way GnRH agonists [esp. Goserelin acetate (Zoladex 3.6mg, AstraZeneca Ltd, UK)] have been used extensively by the author is to change the route of surgery in hysterectomy. If Goserelin 3.6 mg is given every four weeks to a patient with a huge sized fibroid (which could not have been removed vaginally of laparoscopically) pre-operatively for 3-6 months, it decreases the uterine size and a hysterectomy which may have been feasible only by an abdominal route can be performed vaginally. Also, in centres where a morcellator is not available, Goserelin may come to rescue. At times, if a big fibroid is sitting at a place like cervico-isthmic junction, it makes bladder dissection difficult during a laparoscopic hysterectomy. This then requires the hysterectomy to be done by the abdominal route, or may increase the risk of bladder injury if a laparoscopic procedure is attempted. This problem can also be managed by using GnRH agonists for 3-6 months, decreasing the size of fibroid and making a safe laparoscopic procedure feasible. Add-back therapy is not desirable here because adding hormone replacement therapy (HRT) would counteract the desired hypoestrogenic effect needed to shrink the tumor.[33]

Hirsutism

There can be various causes responsible for hirsutism; however, all finally result in excessive androgen production by the ovaries or adrenals or increased sensitivity of the hair follicles to normal circulating androgen levels. Since majority of hyperandrogenic states in women are related to increased ovarian androgen production and are frequently associated with polycystic ovarian syndrome, ovarian suppression with GnRH agonists has been found to benefit hirsute women. Along with substantially reducing hirsutism, GnRH agonist therapy also decreases serum levels of gonadotropins, total testosterone, free testosterone, and androstenedione. Add-back therapy is desirable in this case, as adding sex hormones to GnRH agonist therapy further decreases serum testosterone levels and also reduces the hypoestrogenic side effects of analogues, finally resulting in better results.[35,36] GnRH agonist therapy must be considered for those women with ovarian hyperandrogenism who do not respond adequately to oral contraceptive therapy with or without use of an antiandrogen.

Abnormal uterine bleeding

The spectrum of therapeutic usages of GnRH-a has not left the abnormal uterine bleeding out of it. GnRH agonist suppression of ovarian function has been found to be effective for management of ovarian dysfunction associated with abnormal or acyclic bleeding.[37] Also, endometrial ablation is one of the treatment modalities for menorrhagia. It entails destruction of the entire endometrial layer by means of laser, electrocautery, electrosection, or heating, leaving the uterine cavity intact but scarred and devoid of endometrium. To achieve maximum ablation, the endometrium should be as thin as possible at the start of ablative treatment. Because of their hypoestrogenic effects, GnRH agonists given for a period of around 8 weeks have been found to be very effective in achieving the desired endometrial thinning before the procedure.[38]

Premenstrual dysphoric disorder

Coming back to where we started from! PMDD and premenstrual syndrome (PMS) are common problems of women in reproductive age group. The application of GnRH agonists in treating PMDD and PMS is based both on empiric observations of its efficacy and evidence that cyclic fluctuation in levels of ovarian steroids result in symptom manifestation. Administration of GnRH agonists as long-term treatment for PMS had been reported in several studies, but was limited because of hypoestrogenic side effects, loss of bone mineral density, and cost. Of late, with the advent of add-back therapy, there has been a resurgence of interest in treating this condition with GnRH agonists and as expected has been found to be very useful in markedly alleviating the symptoms of PMDD and PMS.[39]

Few more uses....

GnRH agonists have been put to use in treatment of cancers that are hormonally sensitive and where a hypogonadal state decrease the chances of recurrence. This includes the medical management of prostate cancer in males and also patients with breast cancer. GnRH agonists have also been found to offset the hyperprolactinemia fashioned by microprolactinomas. This effect, it seems that, is not exerted by action on gonadotropins. However, no similar inhibitory effect has been observed in normoprolactinemic women.[40] Several other debilitating conditions associated with or exacerbated by menstrual cycles have been found to be relieved by administration of GnRH agonists. Such conditions include but are not limited to intractable chronic abdominal pain from functional bowel disease and intermittent porphyria.[41,42]

GnRH agonists have also been used in sex reassignment of male to female transsexuals. They have been used in management of severe cases of congenital adrenal hyperplasia (CAH) and combination of GH and GnRH-a have been found to improve final adult height in patients with CAH.[43] Also, of late, women of reproductive age who undergo cytotoxic chemotherapy have been pretreated with GnRH agonists to reduce the risk of oocyte loss during such therapy and preserve ovarian function. GnRH agonists here also switch off the ovaries and put them in quiescence, thereby decreasing the number of actively dividing cells which can undergo damage from chemotherapy.

Diagnostic usages

Injection of native GnRH in human beings elicits an immediate response that may be used to evaluate the status of hypothalamic-pituitary-gonadal function in a variety of neuroendocrine conditions associated with amenorrhea and infertility. This provocative test has been used in an attempt to differentiate hypothalamic disorders from primary pituitary deficiencies.[44-47] Some authorities have also advocated the use of GnRH-a in diagnosis of endometriosis by what is called as "therapeutic trial."[48] This is based on the premise that empiric medical treatment in patients with chronic pelvic pain and a high probability of endometriosis often can avoid a diagnostic surgical procedure.[49]

Posology

Initially, the usage of GnRH agonists was limited to 6 months, but with the advent of add-back therapy, the duration of usage has substantially increased and they have been used even till 2 years. However, it is a matter of debate and controversy and more work needs to be done to find out the maximum safe limit of use. Goserelin and leuprolide are two commonly used GnRH agonists. Goserelin is used in doses of 3.6 mg once every 4 weeks or 10.8 mg once every 12 weeks, and is injected subcutaneously. Leuprolide can be given as a daily dose of 0.5 to 1 mg or monthly depot of 3.75 mg or even can be given 3 monthly in a dosage of 11.25 mg. It can be injected subcutaneously or intramuscularly. Nafarelin is administered by an intranasal spray in the dose of 200 to 400 mcg once or twice daily depending upon the indication of use.

Conclusion

GnRH-a have provided us a powerful therapeutic approach to the treatment of numerous conditions in reproductive medicine. Ongoing basic research and clinical studies will undoubtedly identify additional indications for these drugs. Recent synthesis of GnRH antagonists with a better tolerability profile may open new avenues for both research and clinical applications of these interesting synthetic hormones. It is a call to all stakeholders who are partners in women's healthcare to conduct more and more research into this exciting field of ever-expanding vistas of GnRH-a, and get these hormones their place of honor. Awareness needs to be spread among clinicians so that these drugs can be used to realize their full potential. GnRH-a when used appropriately to their full potential have a potential to be called "wonder drug"!

References

1. World Health Organization Scientific Group, Agents stimulating gonadal function in the human, in Technical Report Series, 1976.
2. Meldrum DR. Clinical management of endometriosis with luteinizing hormone-releasing hormone analogues. Semin Reprod Endocrinol 1985;3:371.
3. Lemay A, Sandow J, Bureau M, Maneux R, Fontaine JY, Merat P. Prevention of follicular maturation in endometriosis by subcutaneous infusion of luteinizing hormone-releasing hormone agonist started in the luteal phase. Fertil Steril 1988;49:410-7.
4. Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: A 12-month study. Lupron Add-Back Study Group. Obstet Gynecol 1998;91: 16-24.
5. Dlugi AM, Miller JD, Knittle J. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: A randomized, placebo-controlled, double-blind study. Lupron Study Group. Fertil Steril 1990;54:419-27.
6. Pickersgill A. GnRH agonists and add-back therapy: Is there a perfect combination?. Br J Obstet Gynaecol 1998;105:475-85.
7. Palomba S, Affinito P, Tommaselli GA, Nappi C. A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. Fertil Steril 1998;70:111-8.
8. Dawood MY, Ramos J, Khan-Dawood FS. Depot leuprolide acetate versus danazol for treatment of pelvic endometriosis: Changes in vertebral bone mass and serum estradiol and calcitonin. Fertil Steril 1995;63:1177-83.

9. Paoletti AM, Serra GG, Cagnacci A, Vacca AM, Guerriero S, Solla E, *et al*. Spontaneous reversibility of bone loss induced by gonadotropin-releasing hormone analog treatment. Fertil Steril 1996;65:707-10.
10. Waibel-Treber S, Minne HW, Scharla SH, Bremen T, Ziegler R, Leyendecker G. Reversible bone loss in women treated with GnRHagonists for endometriosis and uterine leiomyoma. Hum Reprod 1989;4:384-8.
11. Matta WH, Shaw RW, Hesp R, Evans R. Reversible trabecular bone density loss following induced hypo-oestrogenism with the GnRH analogue buserelin in premenopausal women. Clin Endocrinol (Oxf) 1998;29:45-51.
12. Revilla R, Revilla M, Hernández ER, Villa LF, Varela L, Rico H. Evidence that the loss of bone mass induced by GnRH agonists is not totally recovered. Mauritas 1995;22:145.
13. Friedman AJ, Hornstein MD. Gonadotropin-releasing hormone agonist plus estrogen-progestin "add-back" therapy for endometriosis-related pelvic pain. Fertil Steril 1993;60:236-41.
14. Surrey ES. Add-back therapy and gonadotropin-releasing hormone agonists in the treatment of patients with endometriosis: Can a consensus be reached? Add-Back Consensus Working Group. Fertil Steril 1999;71:420-4.
15. Hurst BS, Gardner SC, Tucker KE, Awoniyi CA, Schlaff WD. Delayed oral estradiol combined with leuprolide increases endometriosis-related pain. JSLS 2000;4:97-101.
16. Mukherjee T, Barad D, Turk R, Freeman R. A randomized, placebo-controlled study on the effect of cyclic intermittent etidronate therapy on the bone mineral density changes associated with six months of gonadotropin-releasing hormone agonist treatment. Am J Obstet Gynecol 1996;175:105-9.
17. Palomba S, Orio F Jr, Morelli M, Russo T, Pellicano M, Zupi E, *et al*. Raloxifene administration in premenopausal women with uterine leiomyomas: A pilot study. J Clin Endocrinol Metab 2002;87:3603-8.
18. Moghissi KS, Schlaff WD, Olive DL, Skinner MA, Yin H. Goserelin acetate (Zoladex) with or without hormone replacement therapy for the treatment of endometriosis. Fertil Steril 1998;69:1056-62.
19. Di Vasta AD, Laufer MR, Gordon CM. Bone density in adolescents treated with a GnRH agonist and add-back therapy for endometriosis. J Pediatr Adolesc Gynecol 2007;20:293-7.
20. Ashkenazi J, Dicker D, Feldberg D, Goldman GA, Yeshaya A, Goldman JA. The value of GnRH analogue therapy in IVF in women with unexplained infertility. Hum Reprod 1989;4:667-9.
21. Neven S, Hedon B, Bringer J, Chinchole JM, Arnal F, Humeau C, *et al*. Ovarian stimulation by a combination of gonadotropin-releasing hormone agonist and gonadotropins for *in vitro* fertilization. Fertil Steril 1987;47:639-43.
22. Dodson WC, Hughes CL, Whitesides DB, Haney AF. The effect of leuprolide acetate on ovulation induction with human menopausal gonadotropins in polycystic ovary syndrome. J Clin Endocrinol Metab 1987;65:95-100.
23. Filicori M, Campaniello E, Michelacci L, Pareschi A, Ferrari P, Bolelli G, *et al*. Gonadotropin releasing hormone (GnRH) analog suppression renders polycystic ovarian disease patients more susceptible to ovulation inducation with pulsatile GnRH. J Clin Endocrinol Metab 1988;66:327-33.
24. Markusis V, Goni MH, Tolis G. Therapeutic use of gonadotropin releasing hormone agonists in polycystic syndrome. Ann NY Acad Sci 1993;687:242-9.
25. The Nafarelin European Endometriosis Trial Group. Nafarelin for endometriosis: A large-scale, danazol-controlled trial of efficacy and safety, with 1-year follow-up. Fertil Steril 1992;57:514-22.
26. Fedele L, Bianchi S, Bocciolone L, Di Nola G, Franchi D. Buserelin acetate in the treatment of pelvic pain associated with minimal and mild endometriosis: A controlled study. Fertil Steril 1993;59:516-21.
27. Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75-9.
28. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: Long-term follow-up. Fertil Steril 1993;59:511-5.
29. Batioglu S, Celikkanat H, Ugur M, Mollamahmutoglu L, Yesilyurt H, Kundakci M. The use of GnRH agonists in the treatment of endometriomas with or without drainage. J Pak Med Assoc 1996;46:30-2.
30. Manasco PK, Pescovitz GH, Fenillan PP, Hench KD, Barnes KM, Jones J, *et al*. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. J Clin Endocrinol Metab 1988;67:368-72.
31. Goodpasture JC, Kisei L, Rosenfield R. GnRH agonists in the treatment of true precocious puberty. Infert Reprod Med Clin North Am 1993;4:147-70.
32. Lumsden MA, West CP, Baird DR. Goserelin therapy before surgery for uterine fibroids. Lancet 1987;1:36-7.
33. Friedman AJ, Harrison-Atlas D, Barbieri RL, Benacerraf B, Gleason R, Schiff I. A randomized placebo controlled double-blind study evaluating the efficacy of leuprolide acetate depot in the treatment of uterine leiomyomata. Fertil Steril 1989;51:251-6.
34. Friedman AJ, Rein MS, Harrison-Atlas D, Garfield JM, Doubilet PM. A randomized placebo controlled double-blind study evaluating leuprolide acetate depot treatment before myomectomy. Fertil Steril 1989;52:728-33.
35. Azziz R, Ochoa TM, Bradley EL Jr, Potter HD, Boots LR. Leuprolide and estrogen versus oral contraceptive pills for the treatment of hirsutism: A prospective randomized study. J Clin Endocrinol Metab 1995;80:3406-11.
36. Carr BR, Breslau NA, Givens C, Byrd W, Barnett-Hamm C, Marshburn PB. Oral contraceptive pills, gonadotropin-releasing hormone agonists, or use in combination for treatment of hirsutism: A clinical research center study. J Clin Endocrinol Metab 1995;80: 1169-78.
37. Geisthoevel F, Hills K, Wieacker P, Breckwoldt M, Schultheiss H. Monthly administration of LHRH analogue decapeptyl for long term treatment of ovarian dysfunction and estrogen dependent disorder. Int J Fertil 1989;34:262-70.
38. Sutton CJ, Ewen SP. Thinning the endometrium prior to ablation, is it worthwhile. Br J Obstet Gynaecol 1994;101 Suppl 10:10-2.
39. Mortola JF. Use of GnRH agonists in premenstrual syndrome. Infert Reprod Med Clin North Am 1993;4:51-64.
40. Rubio MA, Cabranes JA, Schally AV, Charro AL. Prolactin lowering effect of luteinizing hormone-releasing hormone agonist administration in prolactinoma patients. J Clin Endocrinol Metab 1989;69:444-7.
41. Mathias JR, Ferguson KL, Clench MH. Debilitating functional bowel disease controlled by leuprolide acetate GnRH analog. Dig Dis Sci 1989;34:761-6.
42. Anderson KE. LHRH analogues for hormonal manipulation in acute intermittent porphyia. Semin Hematol 1989;26:10-5.
43. Lin-Su K, Vogiatzi MG, Marshall I, Harbison MD, Macapagal MC, Betensky B, *et al*. Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2005;90:3318-25.
44. Sandow J. Clinical applications of LHRH and its analogues. Clin Endocrinol (Oxf) 1983;18:571-92.

45. Crowley WF Jr, Filicori M, Spratt DI, Santoro NF. The physiology of gonadotropin releasing hormone (GnRH): Secretion in men and women. Recent Prog Horm Res 1985;41:473-531.
46. Filicori M, Butler JP, Crowley WF. Neuroendocrine regulation of the corpus luteum in the human: Evidence for pulsatile progesterone secretion. J Clin Invest 1984;73:1638-47.
47. Wentz AC. Clinical applications of luteinizing hormone releasing hormone. Fertil Steril 1977;28:901-12.
48. Gambone JC, Mittman BS, Munro MG, Scialli AR, Winkel CA, Chronic Pelvic Pain/Endometriosis Working Group. Consensus statement for the management of chronic pelvic pain and endometriosis: Proceedings of an expert-panel consensus process. Fertil Steril 2002;78:961-72.
49. Ling FW. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. Pelvic Pain Study Group. Obstet Gynecol 1999;93:51-8.

Cite this article as: Magon N. Gonadotropin releasing hormone agonists: Expanding vistas. Indian J Endocr Metab 2011;15:261-7.

Source of Support: Nil, **Conflict of Interest:** Nil.