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EDITORIAL

GnRH ANALOGUES

GnRH (Gonadotropin Releasing Hormone) is synthesized in the hypothalamus. It is released in a pulsatile manner into the hypophyseal portal system to regulate synthesis and release of LH and FSH. The structure of GnRH became known in 1971. Soon superactive analogues with a few hundred times greater potency were developed. It was noted that while single or pulsatile application of GnRH stimulated gonadotropin secretion its chronic use unexpectedly and surprisingly had potent inhibitory effect on gonadotropin secretion. Thus GnRH can be employed for achieveing medical hypophysectomy and gonadectomy which is fully reversible and hence temporary. Although the initial efforts at developing analogues for contraception - unisex contraceptive that can be used by male or female - have failed to deliver practical results, the use of GnRH for conditions dependent on gonadal steroids is well established today. Yet the high cost and lack of free availability have restricted its use in developing countries like ours.

1) INFERTILITY

a) Controlled ovarian hyperstimulation : GnRH is universally employed by ART Centres for ovarian suppression preceeding stimulation. In general long protocols are more effective than short and ultrashort ones. Cummulative pregnancy rates after 3 cycles of ART are increased by 50% when GnRHa suppression preceeds ovarian stimulation. Its other advantages are better planning of treatment cycles, simplification of monitoring, lesser cost and greater convenience to the patient. Ovarian hyperstimulation syndrome, multiple pregnancies, lurking fear of premature menopause, teratogenicity and fear of breast and genital malignancy are acceptable disadvantages of ovarian hyperstimulation. It is hoped that they may be eliminated in near future, by judicious employment of GnRH antagonists.

b) Polycystic Ovaries : High LH in follicular phase in PCOD leads to premature aging of the ova resulting in anovulation, lack of fertilisation and pregnancy wastage. This 'LH Obstacle' is sought to be overcome by using pure FSH or better still recombinant FSH for ovarian stimulation and by employing GnRH suppression preceding stimulation.

2) Idiopathic Central Precocious Puberty : GnRHa can be considered as almost specific treatment for this condition. It arrests gonadarche (gonadotropin dependent pubertal signs) and decreases growth velocity and bone maturation so as to achieve genetically potential height. Incidentally, combination of growth hormone and GnRHa can be used to improve genetic short stature in normal pubertal short children.

3) ENDOMETRIOSIS

Progestogens, danazole and GnRHa all give comparable relief from symptoms in endometriosis with a comparable recurrence in about half of the patients within few months. GnRHa may judiciously be used for selected cases of severe endometriosis especially ones of recurrences. It effectively suppresses endometriosis but does not cure it and carries side effects of temporary menopause including bone demineralisation.

4) FIBROIDS

Generally speaking, asymptomatic fibroids are best left alone while symptomatic ones are treated by myomectomy or hysterectomy. Preoperative employment of GnRHa minimies blood loss during surgery, simplifies surgery in technically difficult situations met with in cases of broad ligament and cervical fibroids, helps laparoscopic myomectomy, facilitates endometrial resections of the fibroids and sometimes enables abdominal hysterectomy to be replaced by vaginal hysterectomy. GnRHa can help postpone surgery (eg. in cases of severe bleeding with extreme anemia) and simplify surgery but does not replace surgery except possibly in perimenopausal women with high surgical risks.

5) HORMONE DEPENDENT MALIGANANCIES :

It is logical that GnRH can be employed as an additional tool besides surgery, chemotherapy and radiotherapy, in the management of cancer of the breast, ovary and endometrium. Similar considerations have prompted the use of GnRHa in treating males with prostatic hyperplasia and prostatic cancer. While managing prostatic cancer cases antiandrogens like flutamide are used with GnRHa in order to avoid the risk of disease flare up at the start of therapy and to neutralise adrenal androgens which constitute 40% of androgens in male.

DISADVANTAGES AND SIDE EFFECTS :

High cost and lack of easy availability are main disadvantages. Side effects depend on patient's age, duration of treatment and extent of estrogen depletion which leads to menopausal symptoms like hot flushes, reduction or loss of libido and bone demineralisation. Six months treatment with GnRHa produces significant decrease in bone mineral density which is usually reversed in 6 to 12 months after stopping treatment. All the same it is better to employ prophylactic add back therapy with premarin 1.25 mg daily. Alternatively tibolone, a synthetic steroid with estrogenic, progestogenic and androgenic properties, can be used in dosage of 2.5 mg daily orally, to prevent bone loss without stimulating endometrium.

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