The Many Applications of GnRH Agonists

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Historical Perspective:

The GnRH decapeptide structure was elucidated by Andrew Schally, for which he was awarded the Nobel prize in 1977.

Just Two centuries ago leading Gynaecologists from all over the world supported the practice of "Ovariotomy" – the surgical removal of normal ovaries for treatment of menstrual madness which equates to today's premenstrual dysphoric disorder (PMDD).

Efficacy of GnRH agonists

The administration of GnRH agonist causes an initial "flare" response followed by downregulation of receptor concentrations. The Hypogonadotrophic hypogonadal state produced by GnRH agonists has been termed as pseudomenopause. However it is a misnomer as the ovaries subjected to GnRH stimulation do not produce estrogen since they do not receive gonadotrophin stimulation and are switched off fpor some time temporarily. . Doses administered subcutaneously are as effective as those given intranasal, intramuscular or even sustained release implants. The major side effects are those of hypogonadism and include hot flashes, decreased libido, vaginal dryness, breakthrough bleeding, and bone mineral depletion. If GnRH therapy is for a prolonged period, then "add back therapy with low dose estrogen –progesterone is recommended (Friedman AJ et al 1993).

In Infertility Management :

In infertility management, multiple follicle development leads to LH surge elicited by premature elevated estrogen concentration leading to confusing away of response. This premature leutinization was the leading cause for failure in infertility management.

The aim of treatment with a GnRH agonist is elimination of the LH surge and fluctuating LH concentration which compromises the outcome in cycles of ovarian stimulation for IVF. In this regard its efficacy appears uncontested whether the treatment is administered using a multiuse Nasal spray, daily injections or depot formulations. Consequently the long course down regulated cycle has become the gold standard for conventional IVF treatment, since the incidence of LH surge is negligible and the subsequent follicular growth which is induced by exogenous gonadotropins is uniform.

However the profound LH suppression can influence estrogen biosynthesis resulting in lower circulating concentration than expected. The potent GnRH agonist induces a sustained release of LH from the pituitary that may last for 24 hrs. This initial "flair up" effect is followed by pituitary desensitization to further GnRH agonist treatment (Casper et al 1980).

The "flair up "effect of the GnRH agonist can be exploited to elicit the start of the follicular growth when GnRH agonist is initiated in the early follicular phase. However due to the physiological consequences of the flair there are chances of formation of functional ovarian cyst which are produced whenever the treatment is started.

In a rare occasion the flare of the LH can rescue the old corpus luteum, luetinization of any advanced small follicles or ovulation of a mature follicle leading to pregnancy. GnRH agonist administered in the

early stages of pregnancy appears to have no undesirable consequences (Janssen S RM et al 2000) .

In woman with reduced ovarian reserve the long protocol can lead to long, arduous and expensive drug treatment with the yield of eggs dictated by the ovarian reserve. In the addition to the use of antagonist protocol in such cases, the use of flare agonist protocol is also beneficial. In such cases to avoid complications mentioned above, pretreatment with progesterone or oral contraceptive is recommended.

The microdose flares protocol in which the agonist use is discontinued prior to the end of follicular phase. One must remember in the flare and microdose flare protocols the GnRH agonist is used to stimulate the ovary and not to eliminate the LH surge.

GnRH agonist can be used for ovulation trigger especially in cases where ovarian hyperstimulation syndrome (OHSS) can occur. These can be given in a single or repeated doses of GnRH agonist (100-500mcg) given subcutaneously or nasally. However these patient had a lower circulating luteal E2 and P4 levels as compared to hCG and consequently had early luteolysis and short luteal phase.

Kolibianabis et al 2005 reported a lower ongoing pregnancy rate when GnRH agonist was used to trigger ovulation and final oocyte maturation as compared to hCG in patients undergoing GnRH antagonist cycles. Although this is attributed to luteolysis there is a strong possibility that this could also influence the oocyte quality and reduce implantation rate. Humaiden et al 2005 also reported a a higher early pregnancy loss in addition to lower pregnancy rates when GnRH agonist was used for trigger.

In Endometriosis :

GnRh agonist are effective in treatment of endometriosis since they induce a hypogonadal state which deprives the disease of estrogen support. Further the amenorrhea induced prevents further new peritoneal seedlings. However once the treatment is stopped the recurrence rate is around 15-20% per year. (Vercellini et al 1993)

In Fibroids:

GnRh due to their ability to produce profound hypoestrogenism has been used for medical management of fibroids. In these cases the fibroids decrease in size over a 3 month period by 40-60%. However it is known to return to pre treatment size by 6 months. Hence the goal for use of GnRH agonist in management of fibroids is preoperative period since reduction the size will help to reduce the blood loss and reduce complications in surgery. (Lumsden et al 1987)

Abnormal Uterine Bleeding:

GnRH agonists have been used on their own for abnormal or acyclical bleeding. It is also preferred as per operative treatment in cases of endometrial ablation to achieve the thinnest endometrial lining before the procedure.

Precocious puberty:

Switching off the ovaries can help delay puberty in young girls with precocious puberty. Long term administration over 12-18 months is safe and effective to achiever prepubertal levels. More striking is the regression of secondary sexual characteristics and cessation of menstrual bleeding. The effects revert once the treatment is stopped and the child follows the expected clinical progression through normal puberty.

Hirsutism:

Although there are various causes for hirsutism, they all result in excessive androgen production by the ovaries, adrenals or increased sensitivity to normal levels. Since majority is due to increased ovarian androgen, GnRH agonist suppression of the ovaries help in the management. Add back

therapy can help to further reduce the testosterone levels in addition to reducing the hypoestrogenic state.

Newer Uses ...

GnRh agonist are nowadays used in the treatment of hormonally sensitive cancers and where a hypogonadal state decreases the chances of recurrence. Eg prostate cancers in men and breast cancers in women. Women of reproductive age who undergo cytotoxic chemotherapy are being pretreated with GnRH agonist to reduce the risk of oocyte loss and preserve ovarian function. Since GnRH switch off the ovaries, they go into quiescence decreasing the number of actively dividing cells which can undergo damage from chemotherapy. Other debilitating conditions associated with or exacerbated with menstrual cycles like chronic pelvic pain, intermittent porphyria are also benefitted I with GnRH administration. .

GnRH has also been used in sex reassignment of male to female transsexuals. , severe cases of congenital adrenal hyperplasia (CAH) and in conjunction with Growth Hormone (GH) achieve and improve the final height in patients with CAH.

References

1. Friedman AJ, Hornstein MD. Gonadotrophin releasing hormone agonist plus estrogen progestin add back therapy for endometriosis related pelvic pain. Fertil Steril 1993;60: 236-41
2. Casper RF, Sheelan KL, Yen SSC. Gonadotropin-estradiol responses to a superactive luteinizing hormone agonist in Women. J. Clin Endocrinol Metab 1980; 50: 179-181
3. Janssen RM, Brus L, Cahill D J et al. Direct ovarian effects and safety aspects of GnRH agonists and antagonists. Human Reprod Update 2000. 6; 505-518.
4. Humaiden P, Bred K Jaer E, Bungun L: GnRH agonist or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles. A prospective randomized study Hum Reprod 2005; 20: 1213-20
5. Vercellini P, Trespidi L, Crosignani PG. A gonadotrophin releasing hormone agonist versus a low dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993;60:75-9.
6. Lumsden MA, West CP. Goserelin therapy before surgery for uterine fibroids. Lancet 1987;1:36-7.