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# GNRH AGONIST VERSUS GNRH ANTAGONIST IN IVF/ET

**By**

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## INTRODUCTION :

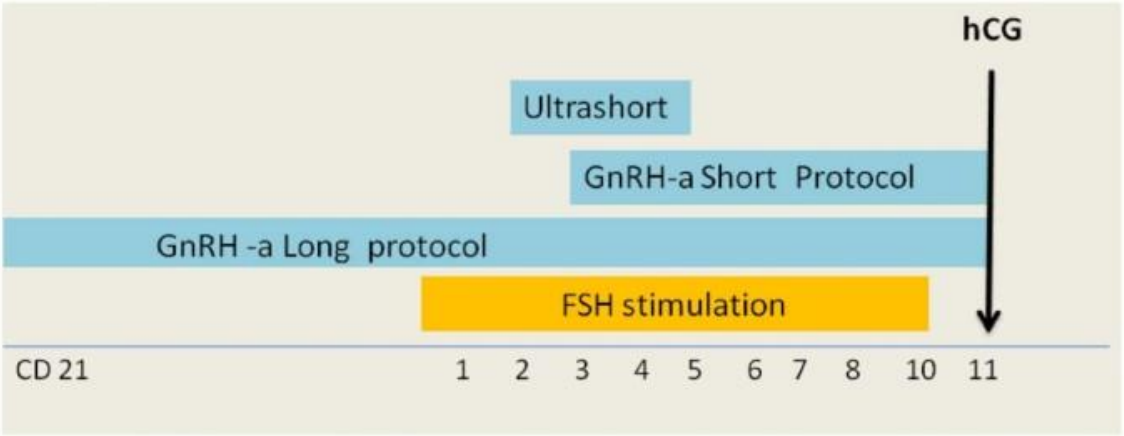
GnRH agonist is associated with increased pregnancy rate. However Patients undergoing IVF/IVSI experience a substantial burden and psychological distress. **GnRH antagonists instead of GnRH agonists**lessen this.There is no difference in terms of live birth rate between GnRH antagonists and agonists. Using antagonists results in **shorter duration of GnRH analogue administration, decreased gonadotrophin requirements and lower incidence of ovarian hyperstimulation syndrome.**

GnRH agonist are the first line in IVF/ET. Several randomized clinical trials demonstrate that they are associated with higher pregnancy rates.Benefitsinclude decreased cancellation rate through prevention of premature LH surge and luteinisation, enhancement of follicular recruitment, allowing the recovery of a larger number of oocytes, and the improvement in routine patient treatment schedule. The **gold standard for ovarian stimulation in young normo-gonadotropic women is recognized as the long protocol**, starting GnRH-a in the mid luteal phase of the preceding cycle.The superiority of the long protocol over the short protocols is proven.

GnRH-a long protocol, induces profound suppression of endogenous release of gonadotropins during the early follicular phase, allowing the early antral follicles to grow co-ordinately in response to exogenous gonadotropins to accomplish simultaneous maturation. This leads to an extended widening of the FSH window, an increased number of recruited mature follicles and a higher number of retrieved oocytes.

**GNRH AGONIST PRO TOCOLS:**

**Long Protocol:** GnRH agonist 0.1 mg starting in follicular phase or luteal phase (Cycle Day 21) of the previuos cycle until hCG administration .
**Short Protocol:** GnRH agonist 0.1 mg starting on day 1 or 3 of stimulation until hCG administration.
**Ultrashort Protocol:** GnRH agonist 0.1 mg administered on day 2–4 of stimulation.



Long protocol has some disadvantages. There is an increased risk of OHSS and side effects like hot flushes, headache, bleeding, and cyst development

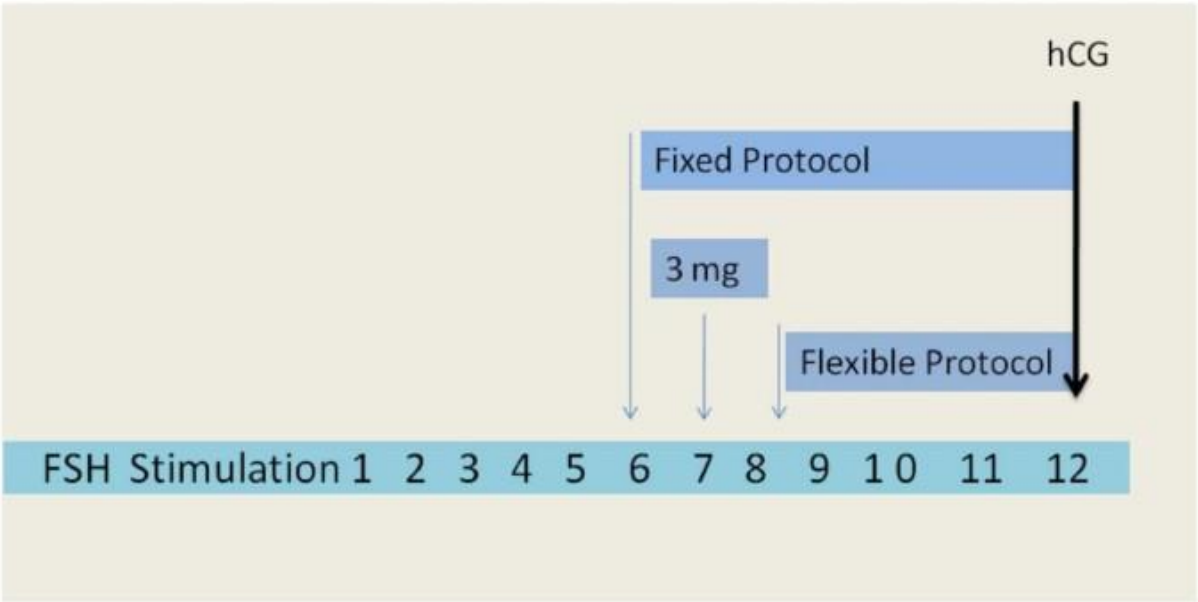
## GNRH ANTAGONISTS PROTOCOLS:

GnRH-ant are currently often used as a second line medication or as first line treatment for patient with lower chances for pregnancy. However recent studies show that they Prevent LH surge resulting in **friendly IVF**. Higher pregnancy rates were found. Multiple pregnancies was also observed when GnRH-ant was administered. Increased duration for administration of gonadotropins was observed in the GnRH-ant group

No significant difference was observed in the clinical pregnancy rates and the live birth rates between the two different regimens

### GnRH antagonist protocols:

**Fixed day 6 protocol:** 0.25 mg GnRH antagonist/daily until hCG administration
**Single dose protocol:** 3 mg GnRH antagonist at day 7 of stimulation
**Flexible dose protocol:** 0.25 mg GnRH antagonist when follicles reach >14 mm



## Comparing GnRH agonist and antagonist protocols :

More than 200 papers have been published with the aim to compare the efficacy of GnRH-ant protocols with GnRH-a long protocol. A meta analysis of these studies showed that the probability of live birth between GnRH-ant and GnRH-a was not significantly different.

## Efficacy and better safety of GnRH ant protocol than GnRH agonist protocol is established with recent studies.

Implantation rate, clinical Pregnancy rate and miscarriage rates were similar in the GnRH-antag regimens as well in GnRH-a long protocol. However a significantly higher number of oocytes and higher proportion of mature MII oocytes was retrieved per patient in the GnRH agonist group.

**SUMMARY :**

| **AGONIST REGIMEN** | **GnRH Agonist long** | **GnRH agonist short and ultra-short** |
|---|---|---|
| **Advantages** | **A**. Stable and low LH and P levels throughout the stimulation phase<br>**B**. Suppression of endogenous FSH levels leading to a follicular cohort of all small follilcles at the initiation of FSH stimulation resulting in a synchronized follicular development | **A**.The ovarian suppression is not excessive<br>**B.** The initial stimulation of the GnRH receptors and consequent secretion of endogenous gonadotropins enhance the effects of the exogenously administered gonadotropins |
| **Disadvantages** | **A**. More time counsuming and complex stimulation protocols<br>**B**. Acute stimulation of gonadotropins and steroid hormones due to the flare up effects<br>**C**. Profound hypoestrogenemia due to downregulation<br>**D**. Risk of complications (OHSS) | Flare up effects in mid-follicular phase |

| | | |
|---|---|---|
| **Clinical comments** | **A**. Increased number of oocytes collected<br>**B**. Additional pregnancy chances from cryo-preserved embryos<br>**C**. Improvement in routine patient treatment schedule | **A.** A microdose GnRHa flare protocol is useful in poor responders<br>**B**. Several microdoses of GnRHa in the flare up protocols have been tested to achieve gonadotropin release and avoid side-effects of the classic flare up protocol |

| **ANTAGONIST REGIMEN** | **GnRH Antagonist fixed** | **GnRH Antagonist flexible** |
|---|---|---|
| **Advantages** | **A**. Immediate, reversible suppression of gonadotropin secretion which avoids effects related to the initial flare up and subsequent down regulation<br>**B**. Initiation of the IVF treatment in a normal menstrual cycle<br>**C**. Endogenous inter-cycle FSH rise rather than FSH suppression, thus resulting in a significant reduction in the effective dosage and shorter treatment, than with GnRH | **A**. Reduced dose of the antagonist is needed<br>**B**. The cohort of follicles have more time to develop thus leading to a higher number of follicles in mid-follicular phase |
| **Disadvantages** | High intercycle endogenous FSH concentrations inducing secondary follicle recruitment and leading to an asynchronous follicular development | LH levels remain unsuppressed during the early follicular phase and enhance $E_2$ production |
| **Clinical comments** | **A**. More IVF cycles to be carried out in a given period<br>**B.** Starting stimulation in patient scheduled for antineoplastic treatments (oocyte cryopreservation) | It makes feasible to tailor stimulation to patients' needs |

## Conclusions:

GnRH-ant regimen is effective in preventing a premature rise of LH and therefore results in a **shorter and more cost-effective ovarian stimulation.** However better follicular growth and oocyte maturation seen with GnRH-a treatment.