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# " YTP UPDATE 2020 "

## Triggers in IVF

### Ovulation triggers in IVF

- In agonist cycles, since there is pituitary down regulation , only HCG can be used as a trigger
- In Antagonist cycles, depending on the Estradiol levels, HCG, GnRH agonist or dual trigger can be used for final oocyte maturation

### Options Available for trigger for oocyte maturation

- URINARY HCG
- RECOMBINANT HCG
- RECOMBINANT LH
- GNRH AGONIST
- KISSPEPTIN

### HCG

Used for over 45 years

### Both LH and hCG bind to the same receptor - LH/hCG receptor

Recombinant HCG is better in :

- › More mature oocytes [9.4 versus 7.1]
  - › Higher luteal progesterone
  - › Better injection tolerance
- Recombinant HCG is better in:

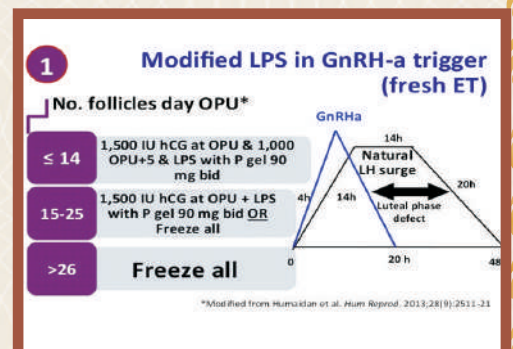
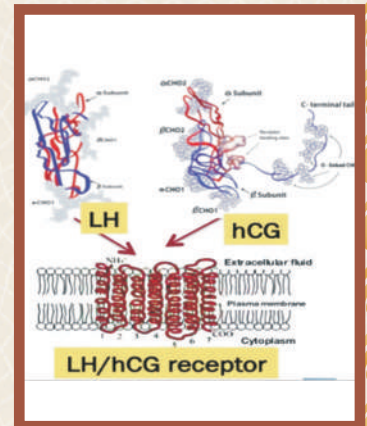
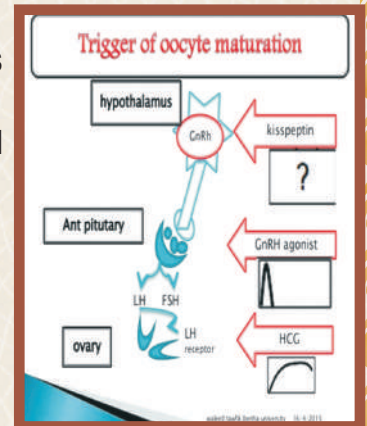
The Problems With HCG As The Trigger

- No FSH surge
- Long half life
- Results in a prolonged luteotropic effect and hence an increased risk of OHSS

### GNRH AND AGONIST

- GnRh induces a flare of both the endogenous FSH and LH like in a natural cycle – more physiological
- Short acting so less chances of OHSS
- More Metaphase II oocytes

The concept of "tailored" luteal phase support:





## The Copenhagen GnRH Agonist triggering Workshop Group – Conclusions

- › Time has come for a paradigm shift in the ovulation triggering concept in ART.
- › GnRHa is more physiological: More number of M11 oocytes
- › Eliminates risk of OHSS, so protocol of choice in oocyte donors and pts for fertility preservation
- › In normo/hyper responders, the difference in PR is non significant, with the current modified LPS. However, an optimal LPS is required
- › An alternative is Segmentation of IVF

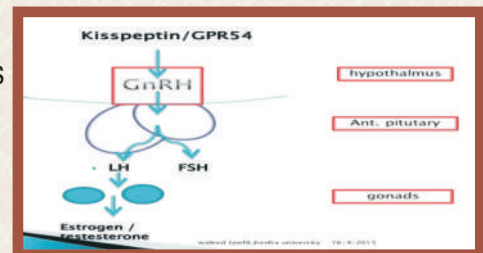
## Recombinant LH as ovulation trigger

- Risk of OHSS is nil
- But, efficacious only at doses of 30,000 iu (400 vials)
- Clinical pregnancy rate of 14% with 5000 iu ofhCG versus 15% with 30000 iu of recombinant LH
- Very expensive, hence abandoned



## Kisspeptins for final Oocyte maturation

- KP are potent stimulators of the hypothalamic-pituitary-gonadal axis
- KP signals directly to the GnRH neurons, which stimulates both LH and FSH from the anterior pituitary to induce a physiological final follicular maturation
- The promising results of a preliminary study need to be further explored in large clinical trials



## Essential Points

- IVF utilizes supra-physiological treatments to simulate many of the physiological processes occurring in the natural menstrual cycle.
- Oocyte maturation is a critical process to the success of IVF treatment, during which the oocyte gains competence for fertilization.
- It is the oocyte completing first meiotic division and progressing to metaphase II oocytes
- It is initiated by LH like exposure that can be provided by triggers like human chorionic gonadotropin (hCG), GnRH agonist, recombinant LH, or kisspeptin.

Why exogenous ovulatory trigger ?

- The natural preovulatory LH surge is inconsistent
- Metaphase 2 oocyte has a relatively short life span
- Hence, a trigger for ovulation is required for timing intercourse or intrauterine insemination or egg collection in IVF

**Wang W et al. J Assist Reprod Genet. 2011 Sep; 28(10): 901–910**

## How do we avoid an early LH surge in IVF: GnRH analogues

- GnRH-agonists administration causes gonadotrophin suppression via pituitary desensitization of GnRH-receptors after an initial short period of gonadotrophin secretion (cycle cancellation drops to 2%)



- GnRH-Antagonists cause immediate gonadotrophins suppression, by blocking the GnRH-receptor avoiding attachment of GnRH molecules

### First and Foremost...

This is the most important injection of the cycle because it's one shot and if we fail to do it right we may reduce the number of MII or cancel the cycle...

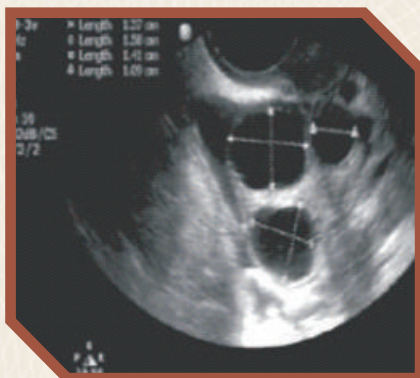
**What criteria must be considered to trigger final follicle maturation?**

#### Follicle Size

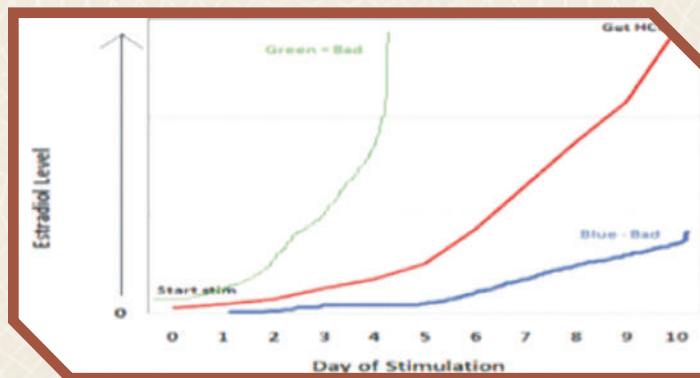
At least 2 follicles >18 - 20 mm  
At least 6-8 follicles >14 -16 mm

#### Estradiol value

Serum levels 1500 - 3000 pcg/ml  
Consider 100-200 pcg/ml/follicle

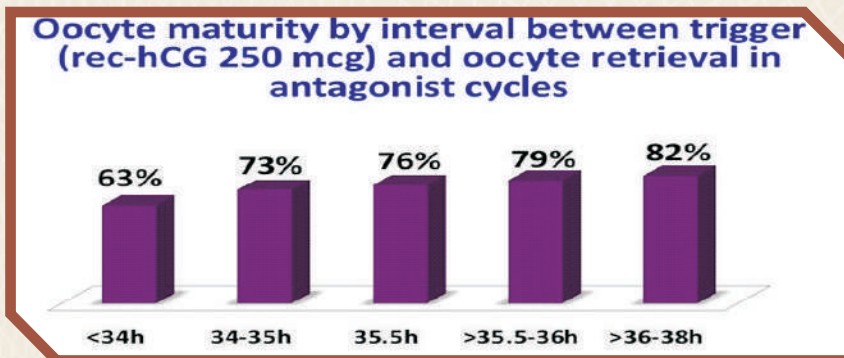


Orvieto R. J Ovarian Res. 2015; 8: 60.



### When ? And Interval

Trigger is given when 3 or more follicles are beyond 17 mm



### Pharmaceutical options for the triggering of final oocyte maturation in ART : summary and recommendations.

Subject	Current Knowledge	Recommendations
GnRHa trigger and oocyte / embryo quality : the oocyte donor model	No significant differences in the number of retrieved oocytes (total and mature), fertilization rates, embryo quality, and pregnancy rates in recipients	First line treatment in egg donors
	Substantial decrease in the treatment burden of the egg donor	

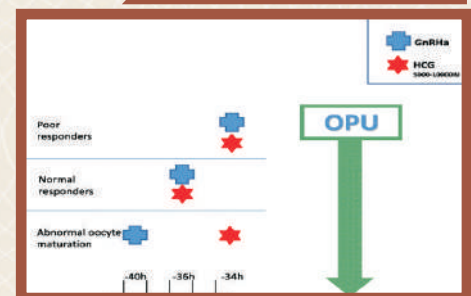


The luteal phase after GnRH-agonist triggering of ovulation	GnRH-agonist triggering is associated with luteal phase insufficiency despite the standard supplementation with vaginal progesterone and estradiol	Luteal phase rescue protocols:
		1500?IU hCG, 35?h after GnRHa trigger*
		IM prog + E2 patches adjusted according to serum levels*
		Repeated bolus of 500?IU hCG
		Freeze-all strategy
OHSS after GnRHa triggering	OHSS cases described in extremely high resppnders who received the 1500?IU hCG rescue protocol	GnRHa trigger and modified luteal support with one bolus of hCG should be used with caution in extremely high responder patients
		Patients with a higher OHSS risk (25 follicles) currently benefit from a freeze-all strategy
	Two OHSS cases reported after GnRHa triggering without any type of luteal phase support	Rare event of unknown etiology
		GnRH, FSH, or LH receptor gene mutations presumably involved
Failure of GnRHa triggering of final follicular maturation	A recent large database analysis showed that the incidence of EFS seems to be similar regardless of whether GnRHa (3.5) or hCG (3.1) triggering is used for final oocyte maturation	Certain forms of pituitary dysfunctions might be responsible for these outcomes in GnRHa triggered cycles
		Most cases of EFS are related to human error, and, thus, a meticulous counseling and instruction of the patient prior to oocyte retrieval is of utmost importance

### Combination trigger

- › Short duration of the LH surge following GnRHa is insufficient to support functional corpora lutea& implantation, there is increasing interest in using a combination of GnRHa with a small dose of hCG.
- › Some investigators have given them simultaneously (termed “dual trigger”), whereas others have administered hCG later to rescue the luteal phase (termed “double trigger”).

### Patient selection & trigger - OPU time



### Indications Of Dual & Double Trigger

- Previous history of > 25% immature oocytes retrieved
- Empty follicle syndrome
- To prevent OHSS in PCOS pts
- To get adequate luteal phase support in PCOS pts
- Poor Responders

### Take Home Messages

- › GnRH agonist trigger - First choice in donors and cancer pts
- › For OHSS free clinic, prefer GnRH agonist trigger & segmentation of IVF treatment
- › DUAL TRIGGER must be considered in poor responders patients with previous poor oocyte yield poor embryo quality
- › Poor responders opt for agonist trigger with modified luteal support or dual trigger to optimize mature oocyte yield and improve pregnancy rates