



kairuki_ivf



MEDICAL CPD HOUSE
Better Medical Knowledge and Skills



KHGIVF

**TRAINING ON
INFERTILITY AND ASSISTED
REPRODUCTION
AT KAIRUKI GREEN IVF**

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DAR ES SALAAM, TANZANIA

16 & 17th SEPTEMBER

**OVERVIEW OF CONTROLLED OVARIAN STIMULATION
(COS) PROTOCOLS IN ART**

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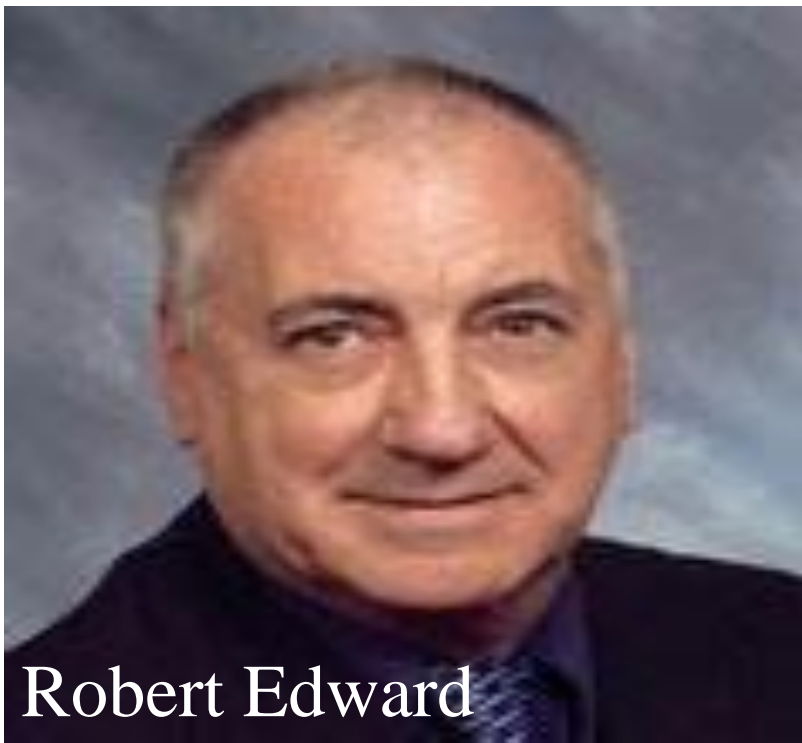
MMED. OBGY & MSc HUMAN CLINICAL EMBRYOLOGY AND ASSISTED CONCEPTION

OUTLINE

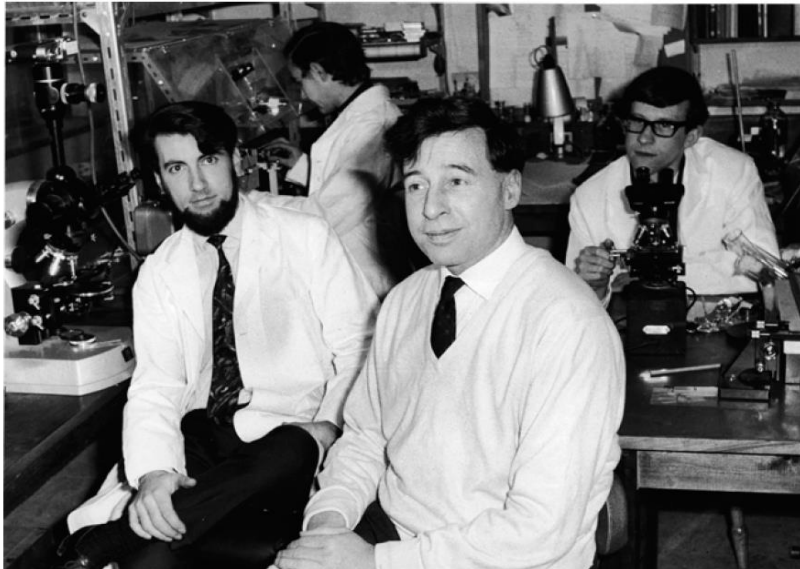
1. HISTORY OF ASSISTANT REPRODUCTIVE TECHNOLOGY
2. AIMS OF CONTROLLED OVARIAN STIMULATION
3. ROLES OF CLINICIANS COS
4. BIOMARKER REVERSE
5. OVARIAN STIMULATION PROTOCOL
6. CONTROLLED OVARIAN STIMULATION PROTOCOL

Assisted Reproduction Technology (ART)/ In-vitro Fertilization (IVF) History (ART) Louise Brown First IVF Baby born in 1978





Robert Edward



Patrick Stepto

- ✓ Thanks to Robert Edward and Patrick Stepto (picture) on 25th July 1978 the first IVF baby was born
- ✓ Her name is Louise Brown now 44 years old
- ✓ The success came after 103 trials
- ✓ 12,000,000 children are born through IVF as reported by Adamson at ESHRE annual meeting.
- ✓ Nobel prize for Physiology or Medicine - 2010
for development of IVF Which is why, said, his estimate of at least 12 million IVF babies

IVF IS A STEPWISE COMPLEX PROCEDURE



Aims of COS in IVF



To recruit a uniform cohort of follicles



To prevent the premature LH surge



To have 5-15 good quality oocytes



To avoid OHSS



Minimal injections



Good endometrial development



Adequate embryos for vitrification



Cost effective and safe

ROLES OF CLINICIANS (Ob/Gyn) in ART

Clinical team

Ob/Gyn

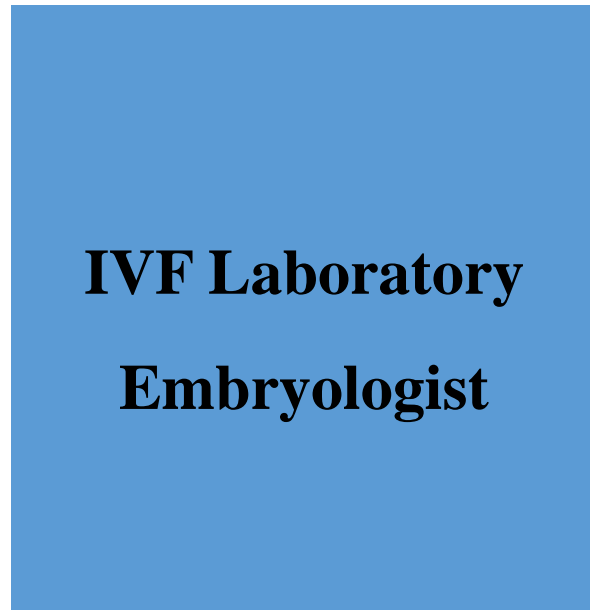


- Embryo transfer
- Luteal phase support



Viable

Embryos

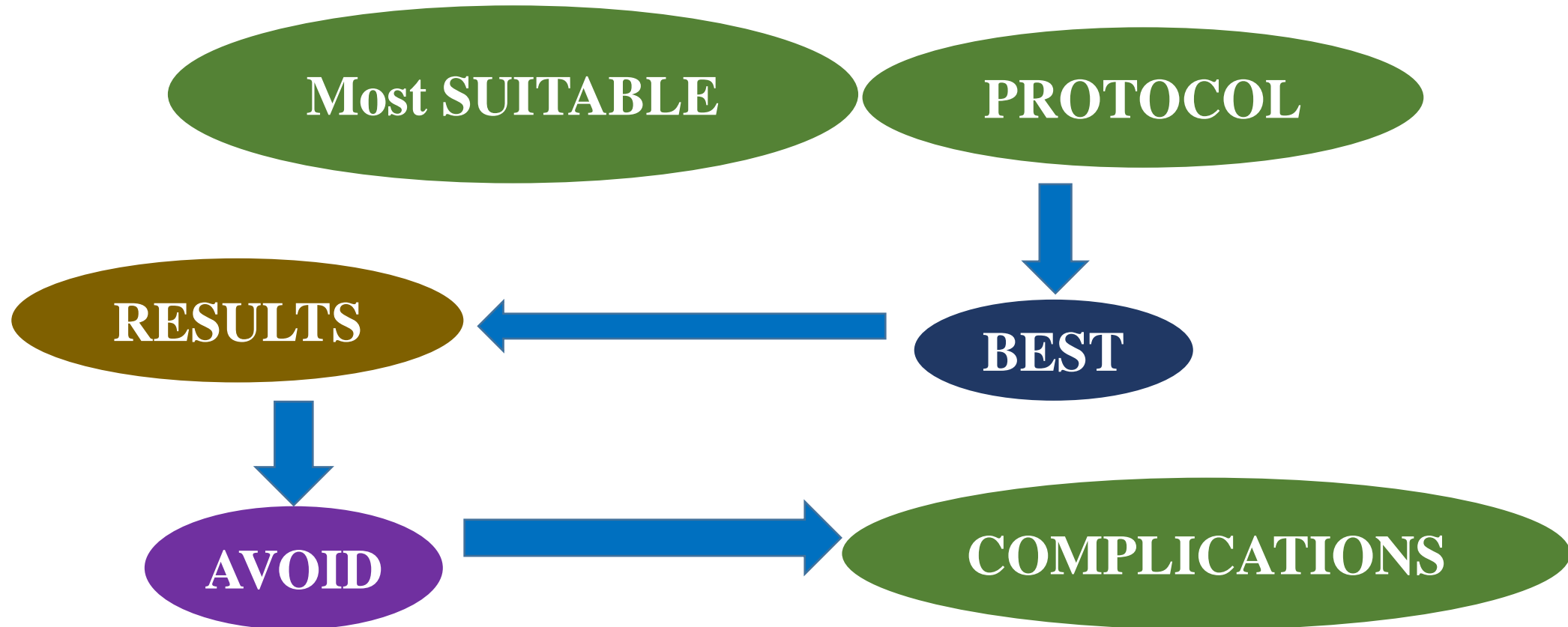


Clinical team Ob/Gyn

- Ovarian Induction/Stimulation

- Monitoring
- Ovum pick-up

Aims of Clinicians (Ob/Gyn) for Ovarian Induction/Stimulation are;



ART PROTOCOL GUIDELINES

Currently, **Tanzania does not have any ART protocol guideline(s).**

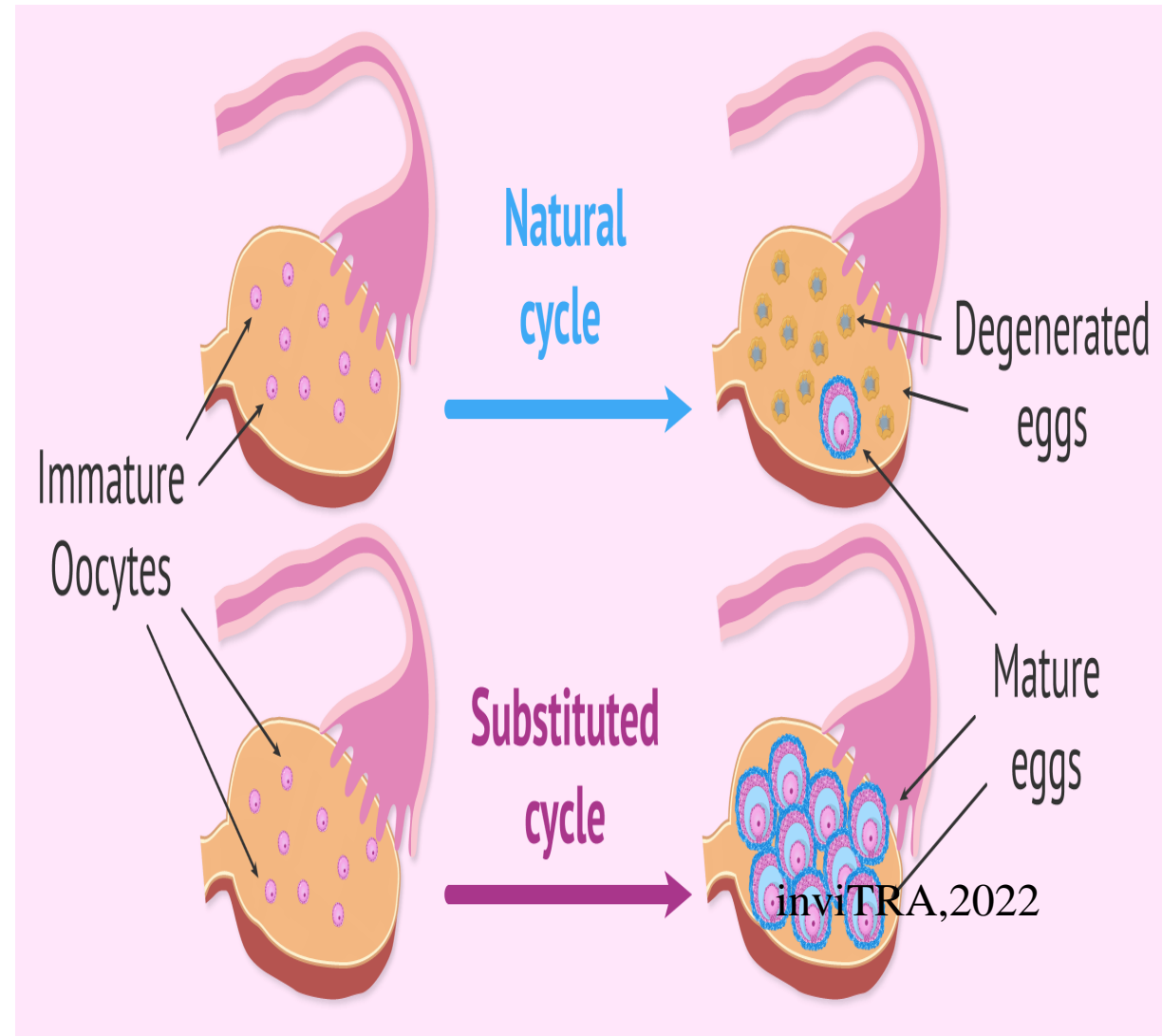
Therefore, we use combined guidelines as shown below

- European Indian Society for Assisted Reproduction (**ISAR**)
- American Society for Reproductive Medicine. (**ASRM**
Society of Human Reproduction and Embryology (**ESHRE**))

Definition of Controlled Ovarian Stimulation (COS)

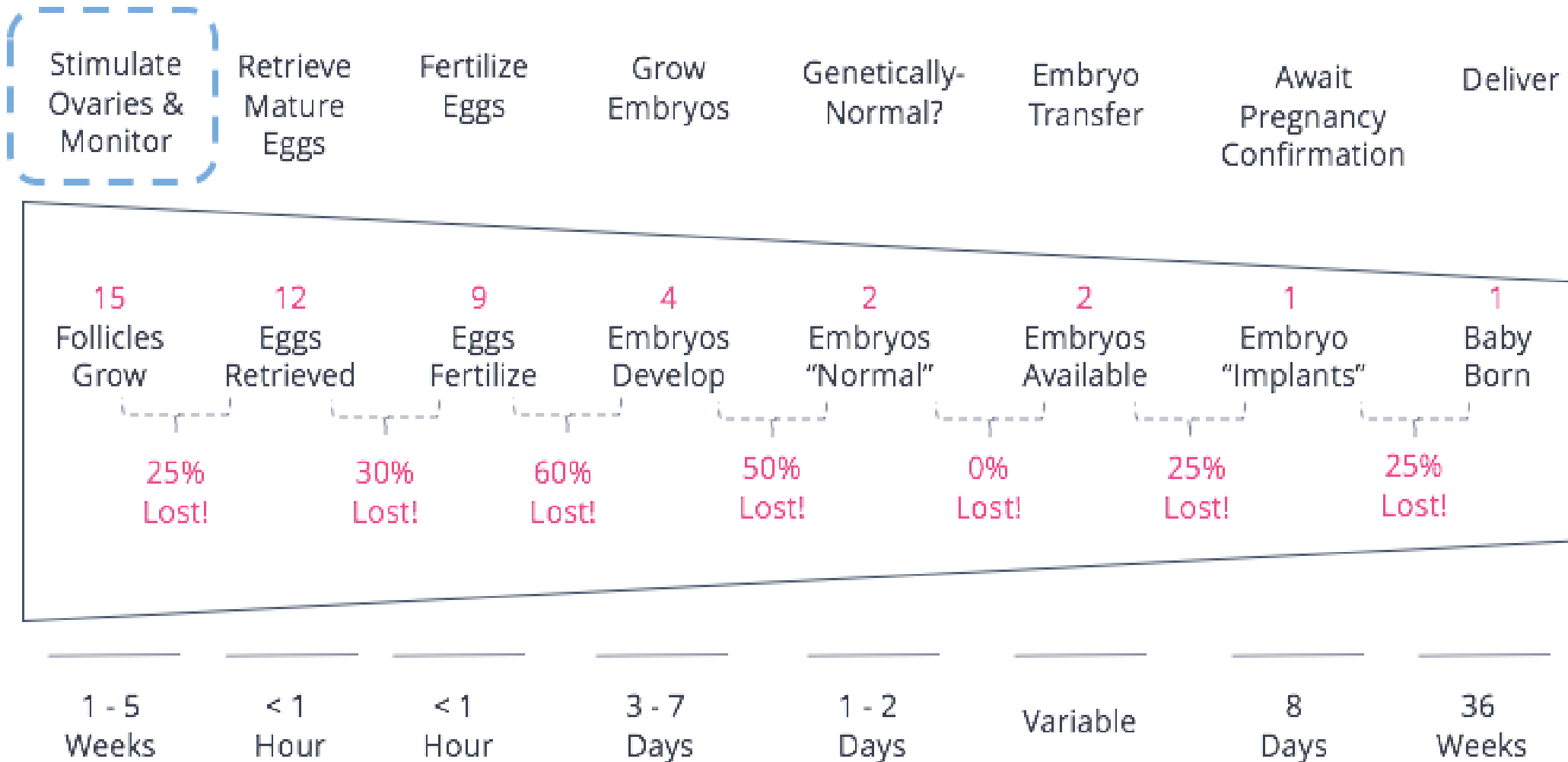
Controlled Ovarian Stimulation is defined as pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two main purposes;

1. Timed intercourse and Intra uterine insemination
2. In ART to obtain multiple oocytes/eggs at follicular aspiration (Zegers-Hoschschild *et al.* , 2017).

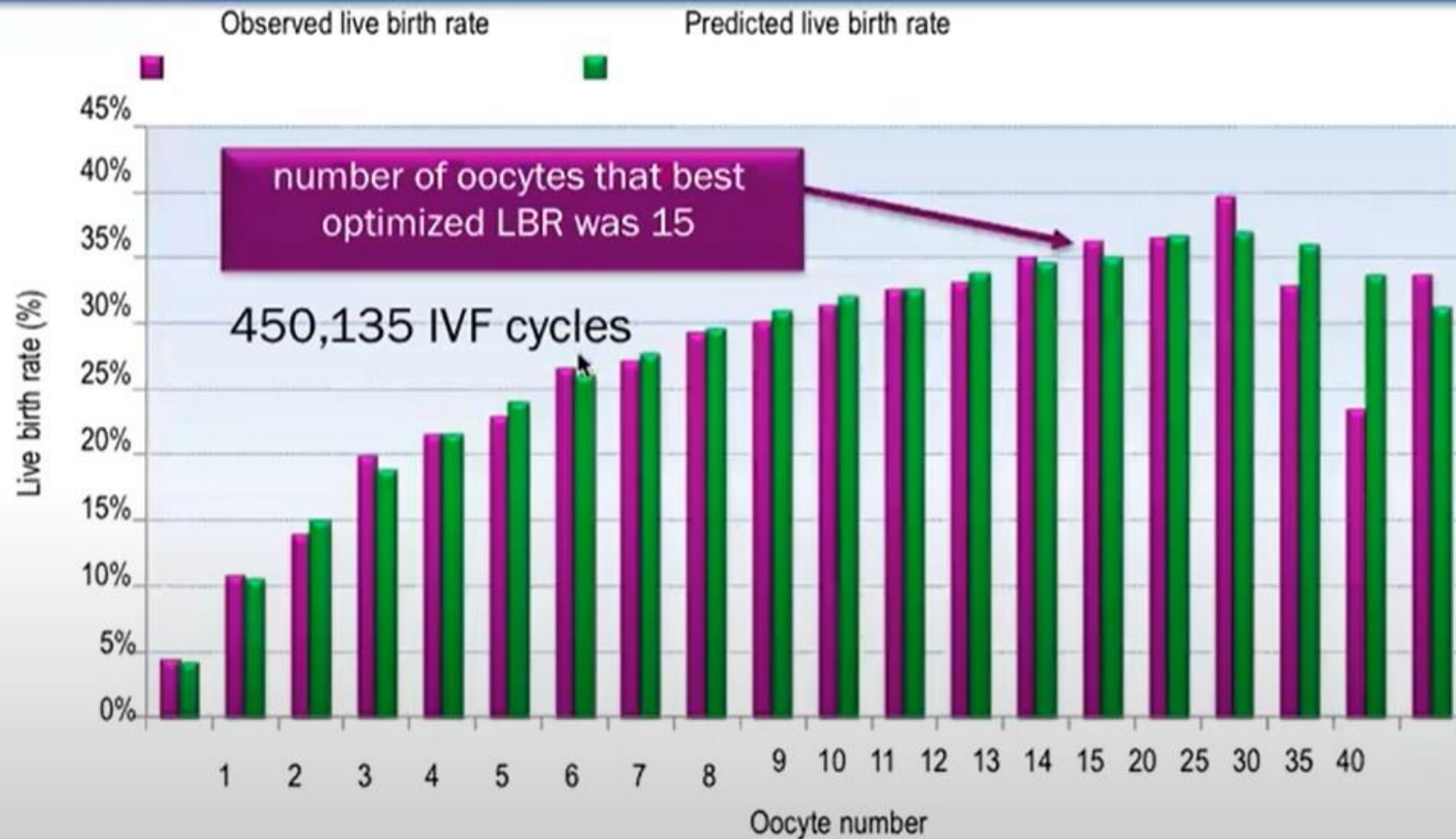


WHY DO WE NEED MORE EGGS/OOCYTES?

Sample Schedule & Funnel For 32 Year-Old IVF Patient



Number of oocytes retrieved and live birth rates



Types of Ovarian Stimulation for ART

	Method	Aim
Natural cycle(unstimulated cycle/spontaneous)	No medication	Single Oocyte
Modified natural	HCG only	Single Oocyte
Mild/Minimum Stimulation	Low dose FSH/HMG Oral compounds (letrozol, clomiphene citrate) GnRH antagonist	2-7 Oocytes
Conventional standard routine COS	GnRH agonist or antagonist Conventional FSH/HMG dose	8 ^{LS} 15 Oocytes

WHAT DO WE EXPECT FROM OVARIAN STIMULATION ?

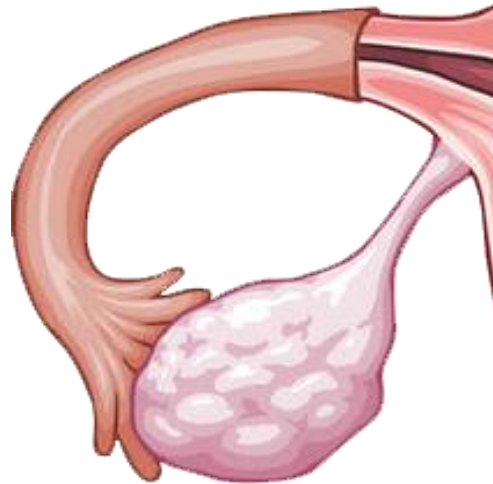


Ovarian Stimulation Responses

Controlled Ovarian Stimulation is expected to produce different types of responses which can be categorized as;

- **High response** is exaggerated response to conventional ovarian stimulation (150-225 IU FSH) characterized by more follicles than expected, generally 18 follicles measuring more 11mm on the day of trigger for maturation, with increased risks of ovarian hyper stimulation syndrome. (Griesinger et al., 2016)
- **Normal response** expected response to conventional ovarian stimulation yielding 4-17 follicles on the day of trigger.
- **Low response** is diminished response to conventional ovarian stimulation generally less than 4 follicles on the day of trigger for maturation.

HOW DO WE TEST FOR OVARIAN RESPONSES?



1. Ovarian Response Testing (Ovarian reserve biomarkers in ART cycles)

- Before commencing ovarian stimulation, we need to have the accurate information of the ovarian reserves.
- Before birth, female fetus has about 6-7 million oocytes (---).
- At birth, the ovary has 1-2 million oocytes available for folliculogenesis. This predetermined number of available oocytes is termed “**the ovarian reserve**”.
- The ovarian response testing can be determined by **Ovarian markers**, which predict ovarian responses.

Importance of ovarian reserve markers

- Counselling patient realistic expectation from stimulation
Oocyte yield
- Avoid iatrogenic complications
- Optimal stimulation strategy
 - ✓ Protocol
 - ✓ Dose of stimulation

OVARIAN RESERVE MARKERS

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graph LR; A((OVARIAN RESERVE MARKERS)) --- B(AFC); A --- C(AMH); A --- D(AGE); A --- E(FSH); A --- F(OTHERS); B --- B1(Antra Follicle Count); C --- C1(Anti-Mullerian Hormones); D --- D1(Ovarian reserves ↓ with age); E --- E1("Day 3(basal) follicle stimulating hormone"); F --- F1["▪ INHIBIN B  
▪ BASAL ESTRADIOL  
▪ BMI"];
```

AFC

Antra Follicle Count

AMH

Anti-Mullerian Hormones

AGE

Ovarian reserves ↓ with age

FSH

Day 3(basal) follicle stimulating hormone

OTHERS

- **INHIBIN B**
- **BASAL ESTRADIOL**
- **BMI**

Indications for ovarian reserve testing

1. Women undergoing infertility evaluation / treatment
2. Individualization of COS protocols and dosing for ART
3. History of premature ovarian insufficiency or failure or early menopause
4. PCOS
5. Women considering elective (social) egg freezing
6. Oocyte donors
7. Fertility preservation before and after gonadotoxic treatment
8. Preoperative prior to ovarian surgery in reproductive age women
9. Women with BRCA-1 or FMRI premutation

Gold Standard markers

AGE

AFC

AMH

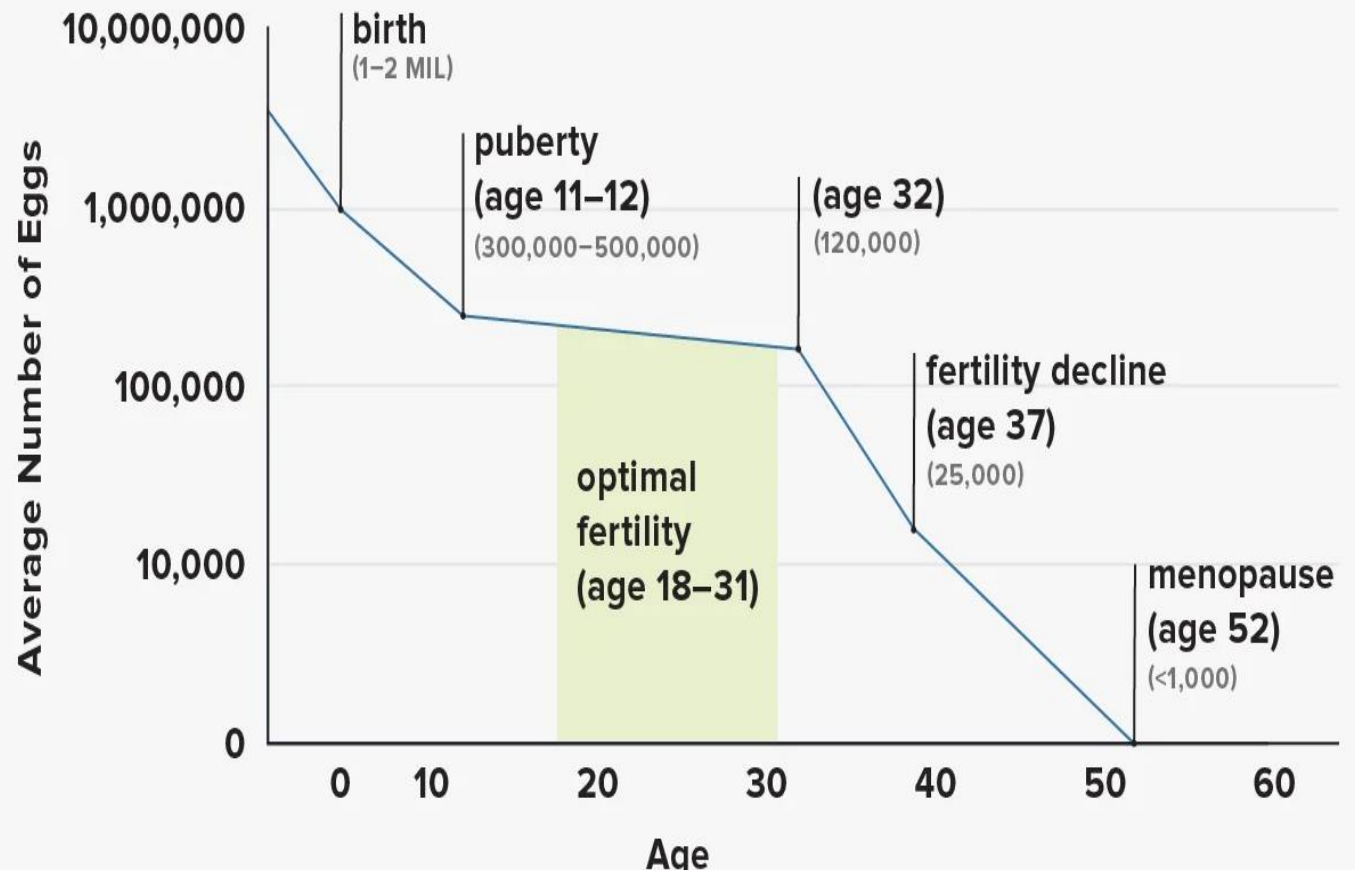
These are the most important biomarkers

AGE DEFINING OVARIAN RESERVES

According to the American College of Obstetricians and Gynaecologists (ACOG);

- A female fetus typically has around 6–7 million eggs at 20 weeks of gestation
- Drops to 1–2 million at birth.
- The number of immature egg cells decreases by around 11,000 each month before puberty.

How many eggs does a woman have?



Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach

Simone L. Broer^{1,2,*†}, Jeroen van Disseldorp^{1,2,†}, Kimiko A. Broeze^{1,2}, Madeleine Dolleman^{1,2}, Brent C. Opmeer^{1,2}, Patrick Bossuyt^{1,2}, Marinus J.C. Eijkemans^{1,2}, Ben-Willem J. Mol^{1,2}, and Frank J.M. Broekmans^{1,2} on behalf of the IMPORT study group^{**}

GnRH analogues and the fine tuning of the gonadotrophin dose on the basis of potential ovarian response in every single woman can allow for a safer and more effective IVF practice.

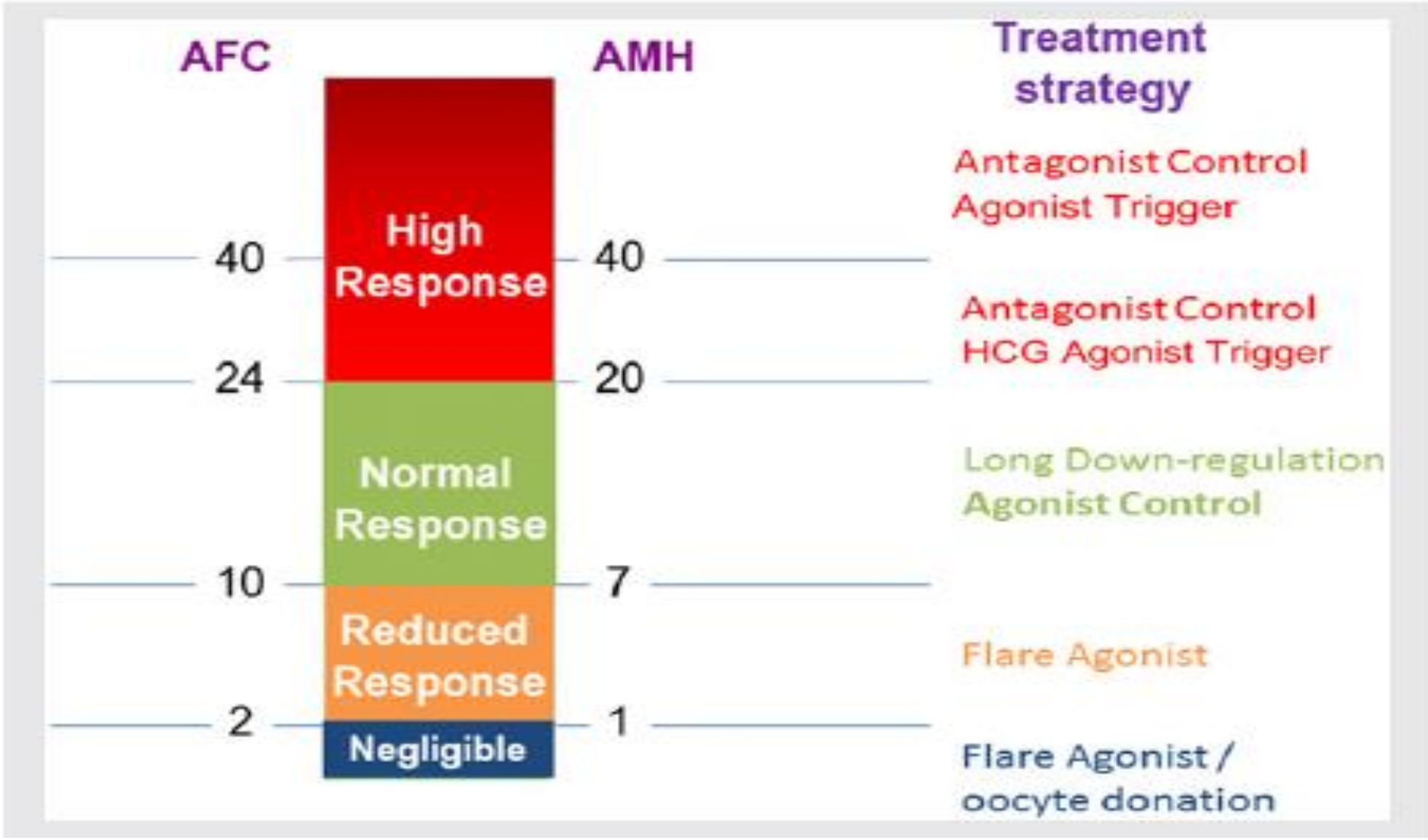
BACKGROUND: Although ovarian reserve tests (ORTs) are frequently used prior to IVF treatment for outcome prediction, their added predictive value is unclear. We assessed the added value of ORTs to patient characteristics in the prediction of IVF outcome.

METHODS: An individual patient data (IPD) meta-analysis from published studies was performed. Studies on FSH, anti-Müllerian hormone (AMH) or antral follicle count (AFC) in women undergoing IVF were identified and authors were contacted. Using random intercept logistic regression models, we estimated the added predictive value of ORTs for poor response and ongoing pregnancy after IVF, relative to patient characteristics.

RESULTS: We were able to collect 28 study databases, comprising 5705 women undergoing IVF. The area under the receiver-operating characteristic curve (AUC) for female age in predicting poor response was 0.61. AFC and AMH each significantly improved the model fit (P -value <0.001). Moreover, almost a similar accuracy was reached using AMH or AFC alone (AUC 0.78 and 0.76, respectively). Combining the two tests, however, did not improve prediction (AUC 0.80, $P = 0.19$) of poor response. In predicting ongoing pregnancy after IVF, age was the best single predictor (AUC 0.57), and none of the ORTs added any value.

CONCLUSIONS: This IPD meta-analysis demonstrates that AFC and AMH clearly add to age in predicting poor response. As single tests, AFC and AMH both fully cover the prediction of poor ovarian response. In contrast, none of the ORTs add any information to the limited capacity of female age to predict ongoing pregnancy after IVF. The clinical usefulness of ORTs prior to IVF will be limited to the prediction of ovarian response.

Ovarian reserve biomarkers in ART cycles treatment strategy



**WHAT IS THE FIRST STEP TO ACHIEVE
DESIRED CONTROLLED OVARIAN
STIMULATION ?**



. Ovarian Pre-treatment

Ovarian pre-treatment is a treatment done before the cos to ensure a successful cycle. It is aimed at;

✓ Suppression or reduction of LH or FSH secretion prior

gonadotropin stimulation in IVF.

✓ synchronization of follicular development to prevent

occurrence of early large follicle or spontaneous LH surge.

✓ Reduction of cysts formation.

✓ Pretreatment is also used for scheduling IVF cycle or

batching which is cost effective, may benefit clinician

Drugs used for pretreatment can be;

1. Oral Contraceptive Pills (OCP) 10 -15 days
2. PROGESTIN, i.e. NORETHISTERONE (7-10 Days before expected menses)
3. OESTROGEN (7- days before menses)
4. ANTAGONIST, i.e. CETRORELIX three days front the day of menses

HOW DO WE KNOW THAT DOWN REGULATION WAS ACHIEVED?



BASELINE HORMONES BEFORE STARTING STIMULATION



Remember
the Rule of
5

01

ESTRADIOL < 50pg/ml

02

PROGESTERONE <0.5ng/ml

03

FSH < 5IU

04

LH <5IU

05

ENDOMETRIAL THICKNESS <5MM

PROTOCOLS FOR OVARIAN DOWNREGULATION (LH SURGE PREVENTION) & CONTROLLED OVARIAN STIMULATION

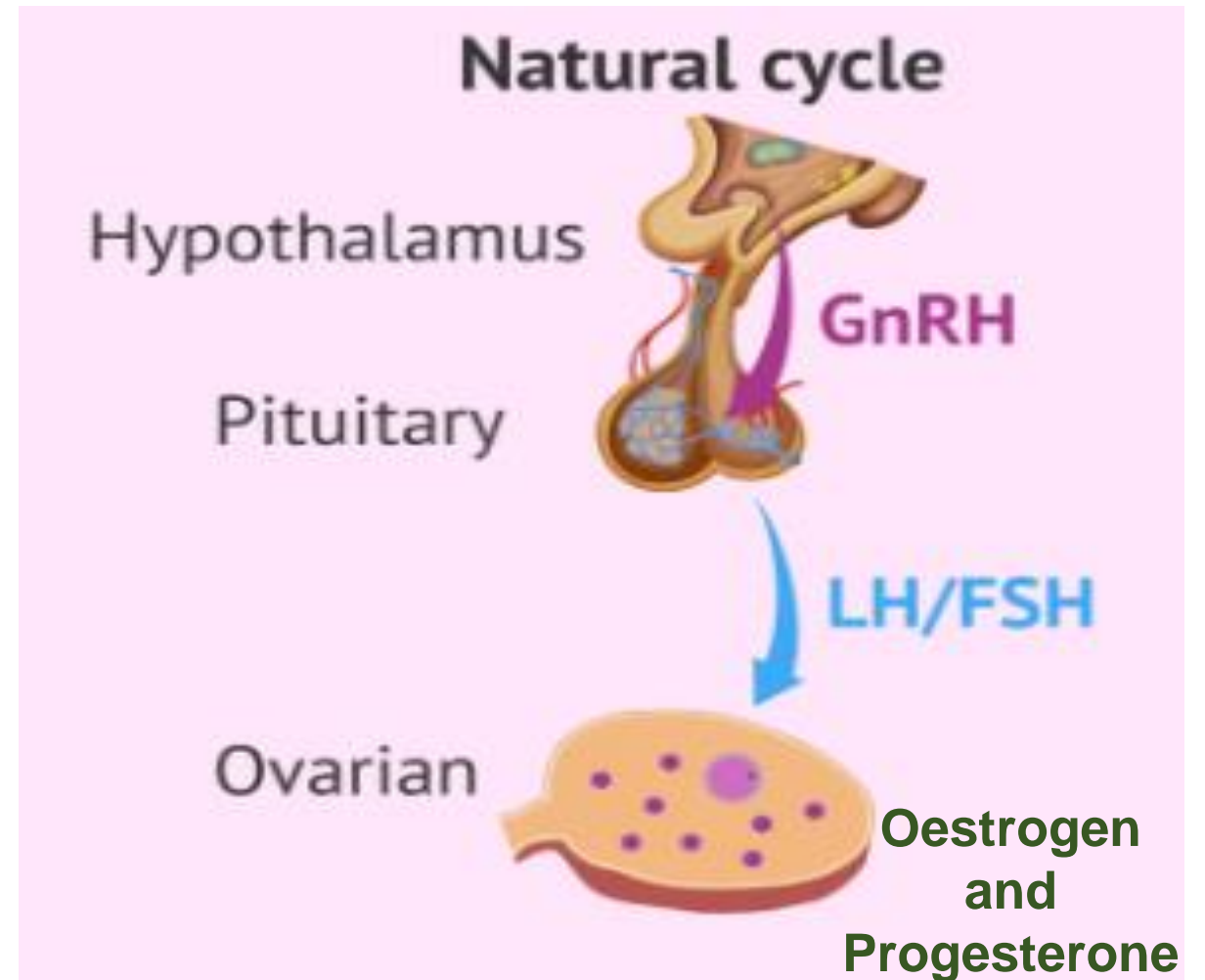
- IVF /ICSI Uses two main protocols for ovarian downregulation
- 1 GnRH AGONIST PROTOCOL
- 2 GnRH ANTAGONIST PROTOCOL
- All aimed at down regulation of the pituitary therefore controlling premature LH surge until full oocyte maturity can be reached.

They are usually administered at the same time or before gonadotrophins hormones (FSH, LH, and HMG) during COS.

- Gonadotrophic function

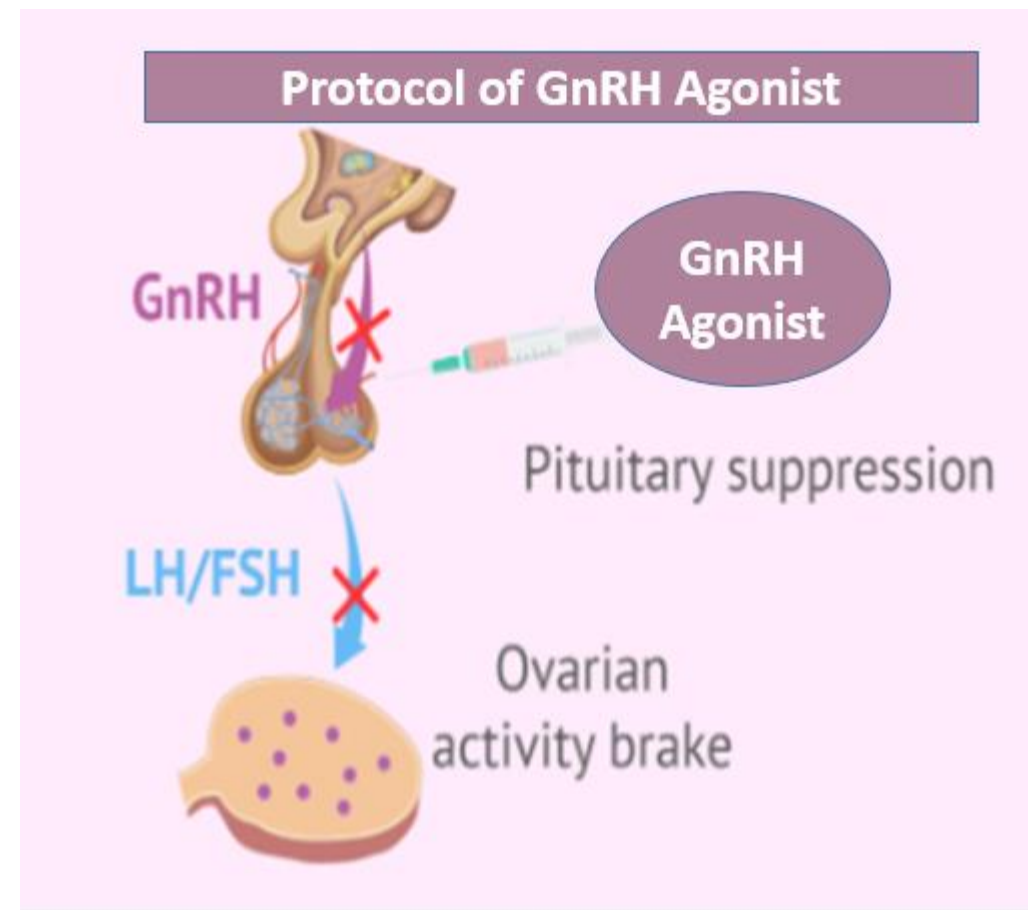
Mechanism of Action of GnRH agonist and antagonist

- Action of native GnRH on a gonadotrophin receptors in the pituitary results in FSH and LH secretion.
- FSH and LH, in turn, stimulate the gonads to produce steroid hormones (Oestrogen and Progesterone).



1. GnRH agonist

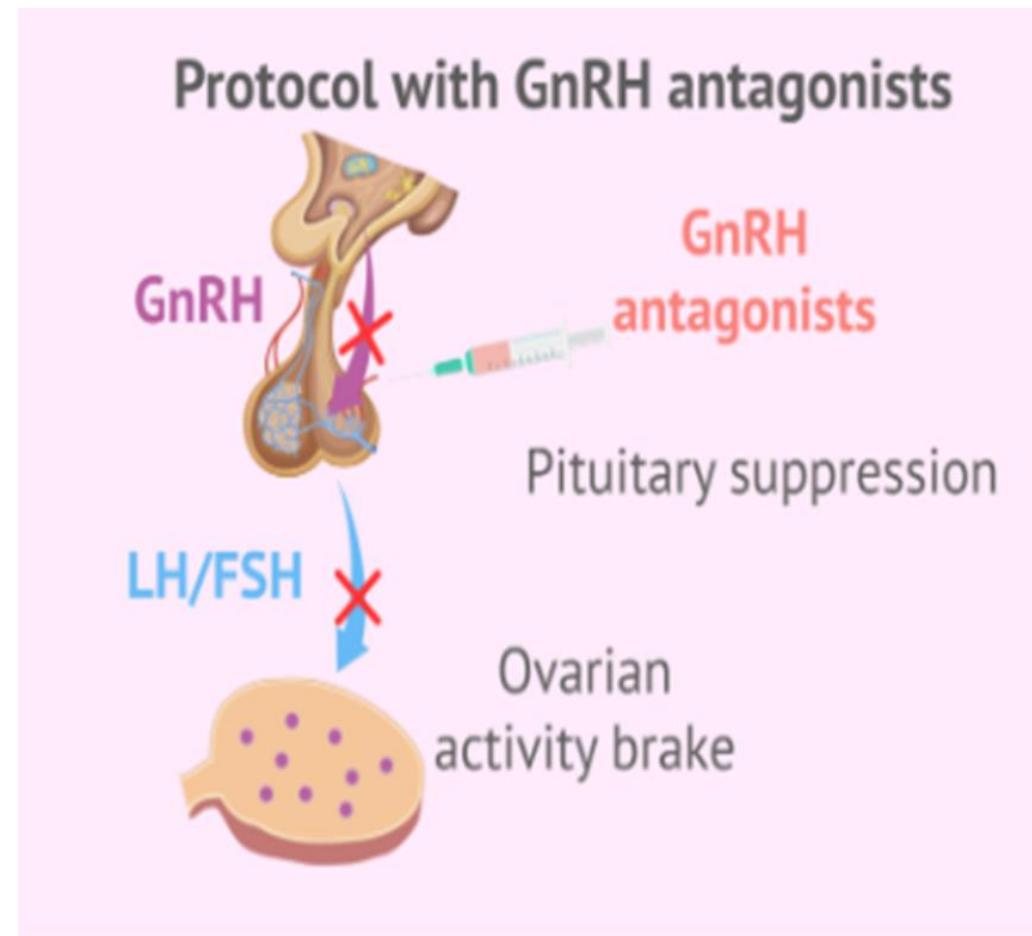
- GnRH agonist binds to the gonadotrophin receptor to produce an initial stimulation of FSH and LH (Flare), but subsequently suppression of gonadotropins occurs, with the resulting suppression of gonadal steroid production. Examples: **Leuprorelin**, Buserelin, Histrelin, **Goserelin**, Deslorelin, Nafarelin
And Triptorelin



2. GnRH antagonist

- GnRH antagonist binds to the gonadotrophin receptor to stimulate an immediate downregulation and desensitization with resulting suppression of gonadotropin secretion and gonadal steroid.

Examples e.g. **Cetrorelix**, **ganirelix**,
elagolix



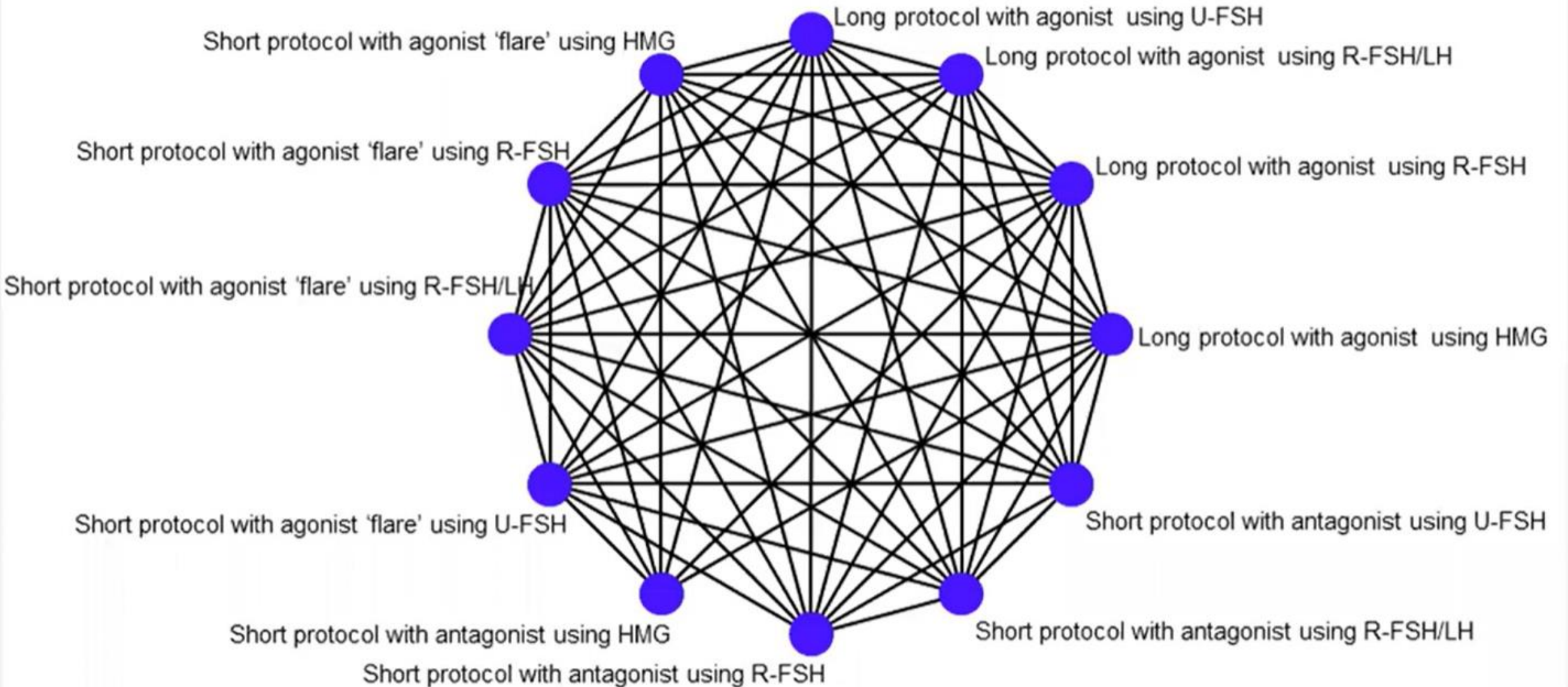
Gonadotropins

The gonadotropins are peptide hormones that regulate ovarian and testicular function and are essential for normal growth, sexual development and reproduction. The human, gonadotropins include follicle stimulating hormone (FSH) and luteinizing hormone (LH).

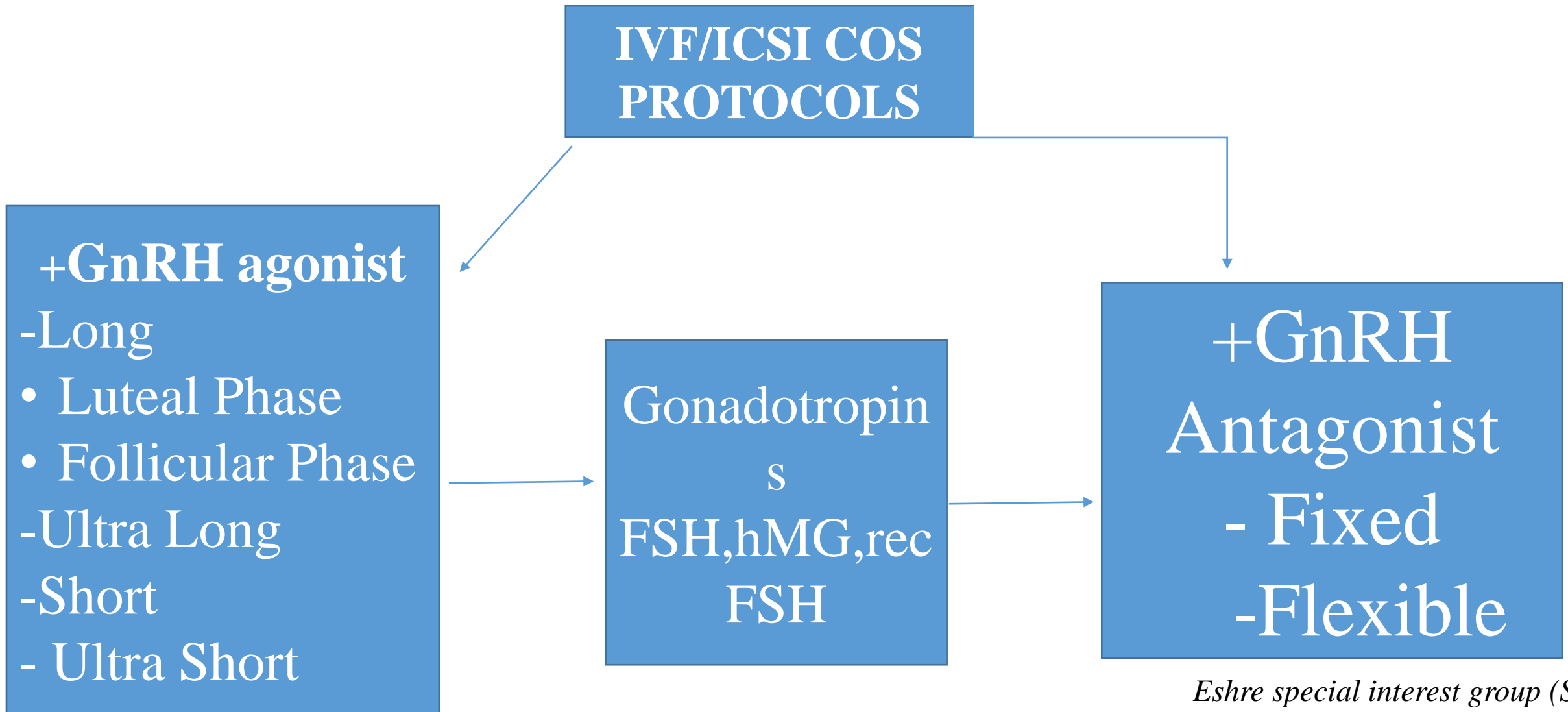
Commonly used gonadotropins in ART are;

- Human Menopausal gonadotrophin (hMHG)
 - Highly purified hMG (HP-hMG)
 - Urinary human FSH (u-hFSH)
 - Urinary human FSH (u-hFSH)
 - Recombinant Human Follicle Stimulating Hormone (rec-hFSH)
- ✓ Alpha
- ✓ Beta

CHOICE OF THE SUITABLE PROTOCOL



PROTOCOLS FOR OVARIAN DOWNREGULATION (LH SURGE PREVENTION) & CONTROLLED OVARIAN STIMULATION



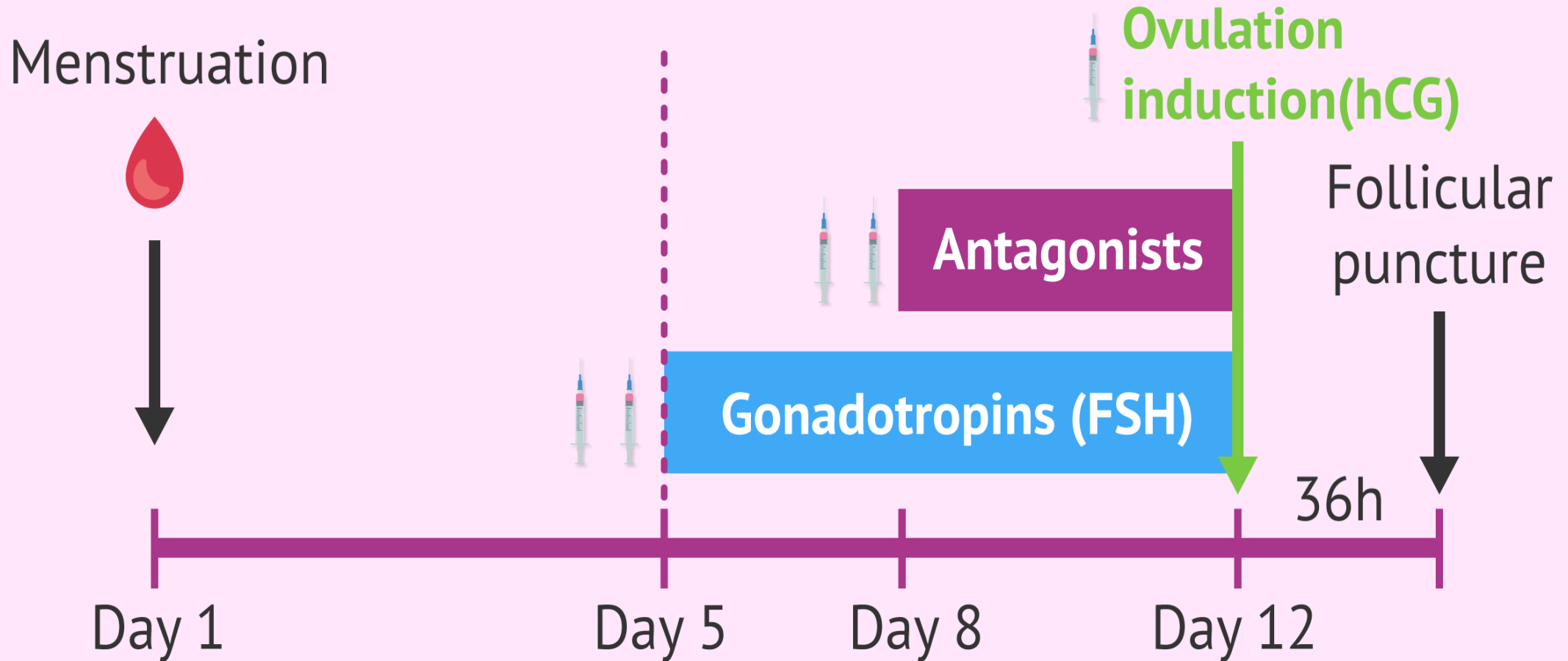
Eshre special interest group (SIG)

CHOICE OF THE SUITABLE PROTOCOL STRATEGY

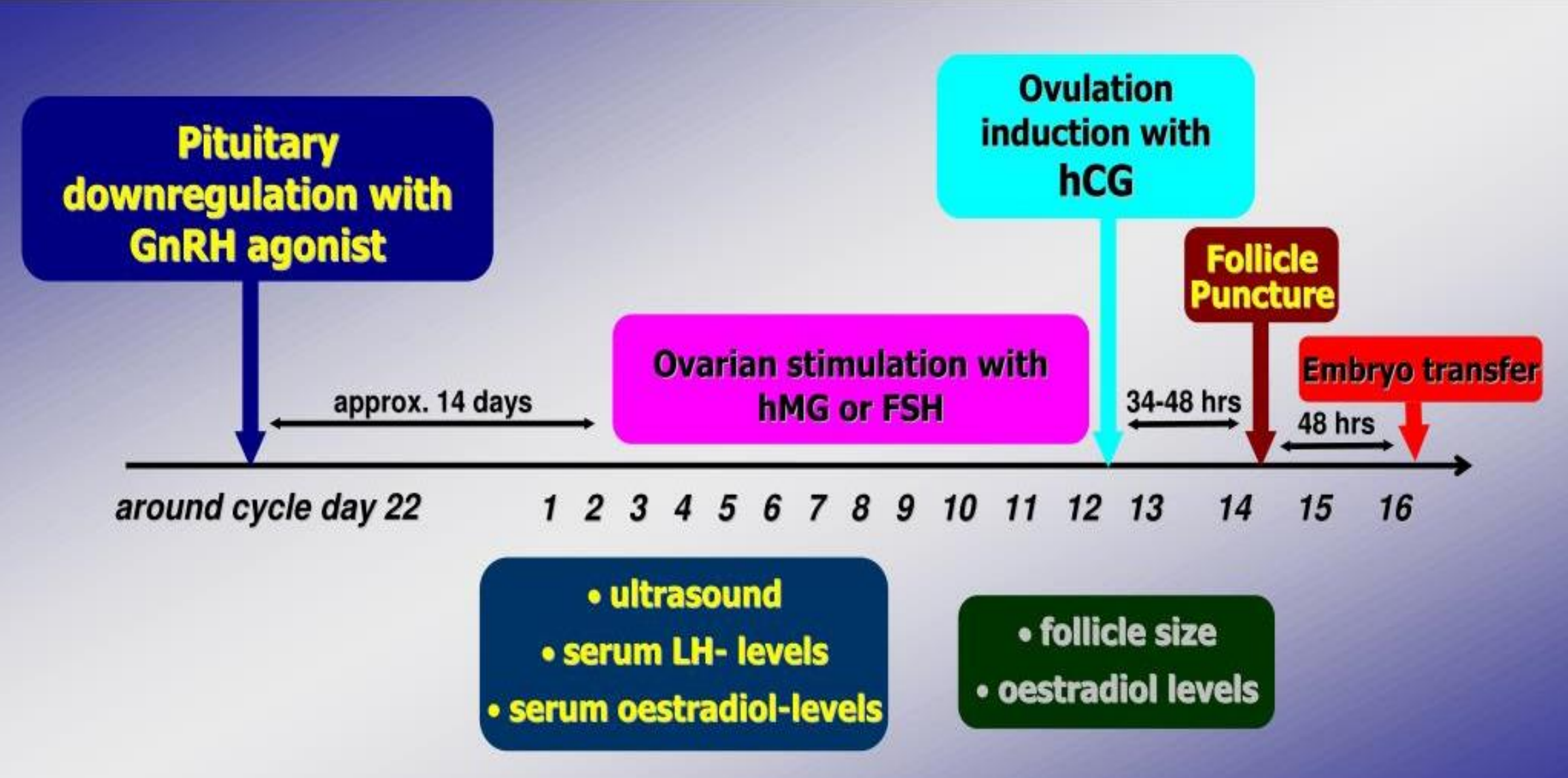
- The choice of the strategy for cos depend on the type of the expected responses (high, normal or low) following the patient evaluation as mentioned earlier.
- **HIGH RESPONDERS** (PCOS, YOUNG PATIENT)
- **NORMAL RESPONDERS** 32-35 AGE GROUP
- **LOW RESPONDERS** 37 AND ABOVE

Eshre special interest group (SIG)

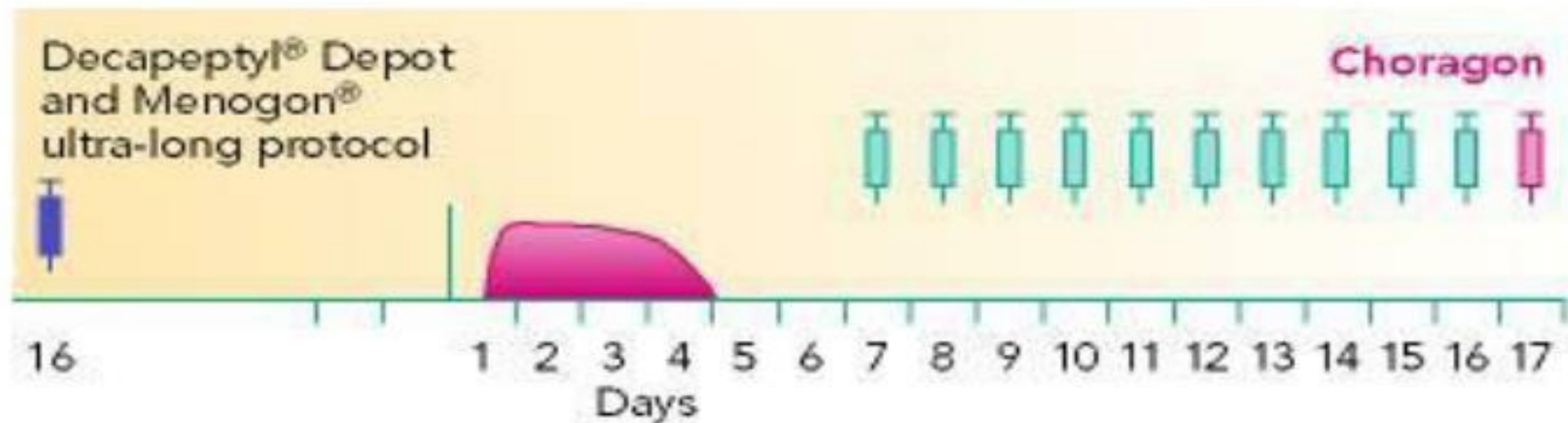
ANTAGONIST PROTOCOLS (FIXED & FLEXIBLE PROTOCOL)



LONG AGONIST PROTOCOL

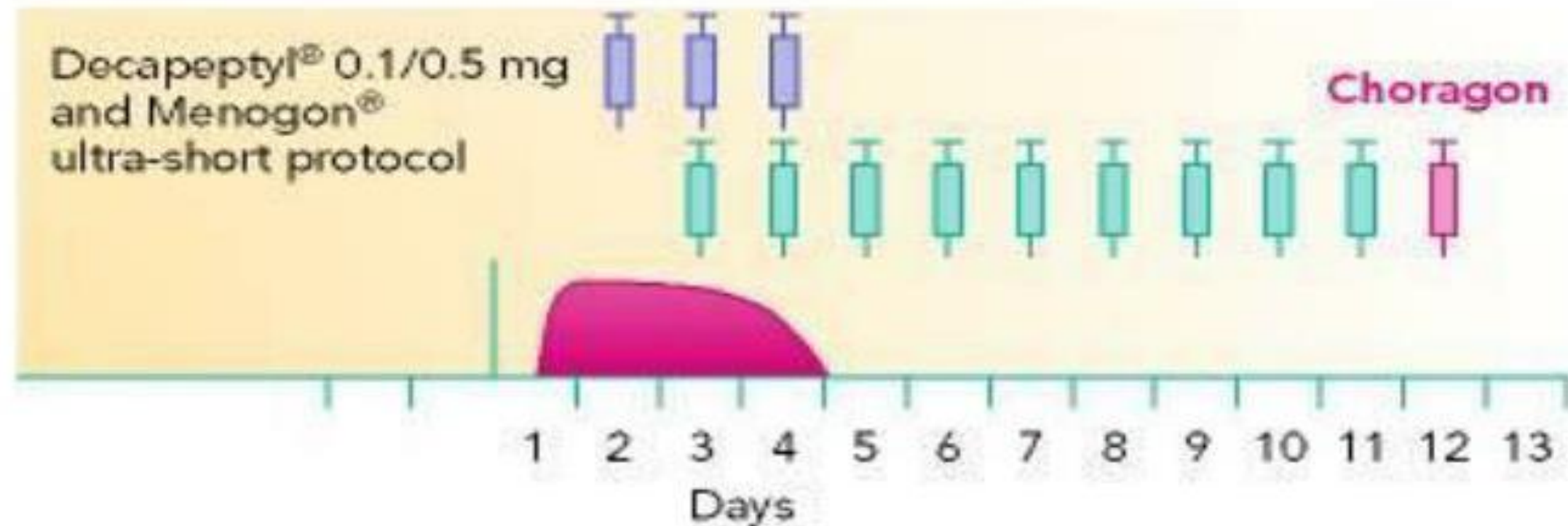


The ultra-long protocol



- ↪ **GnRH agonist administered on the first day of the luteal phase, directly after ovulation in the preceding cycle**
- ↪ **Helpful in patients where LH and FSH persistently released during the standard 'long' protocol**

The ultra-short protocol



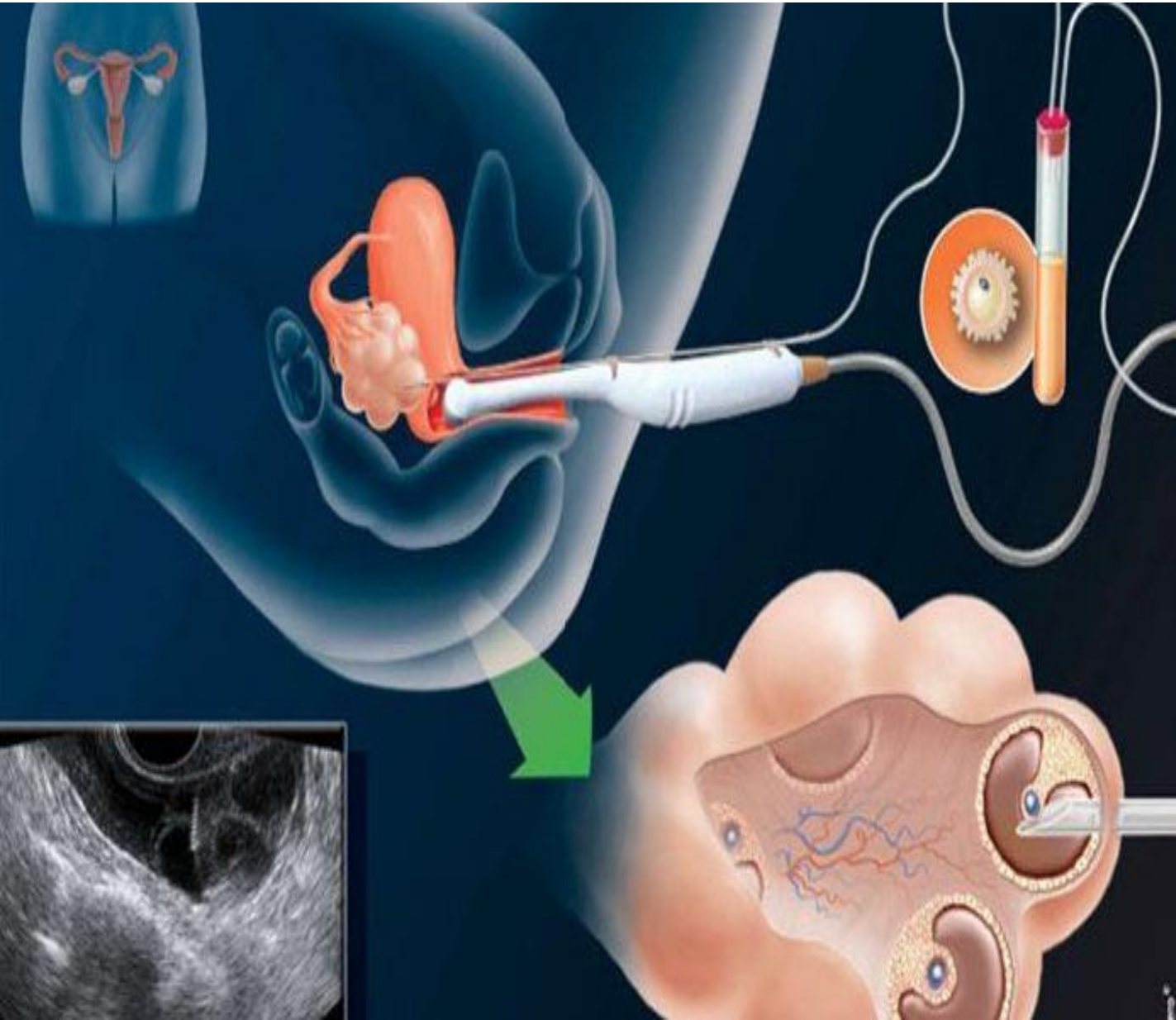
↪ **Treatment modality counts on prolonged pituitary desensitisation beyond the short period of GnRH agonist administration**

THE TRIGGER SHOT



- ✓ The trigger shot is an inj given to mature the eggs 36 hours before they are picked from the ovary.
- ✓ After the injection you will go home and wait for 34-35 hours and you will return to the facility for the pick up .

EGGS PICK UP



✓ Eggs pick up or will be done on 2nd and 3rd TH OR 4TH July 2023.

✓ Pick up or eggs collection is done 34-35 hours following HCG injection.

✓ The procedure is done under anaesthesia

✓

EGGS PICK UP



✓ The ovum pick procedure is ultrasound guided, It done using the needle that is attached on the ultrasound probe by using a biopsy guide, which will be inserted in the vagina, and the needle will be advanced to the ovary.

✓ Then aspiration of all follicles will be done, and the follicular fluid containing eggs will be taken to the iIVF laboratory for retrieval od matured eggs by the Embryologist.

CONCLUSION

- Ovarian reserve markers are very important part of controlled ovarian stimulation.
- Pre-treatment before controlled ovarian stimulation should always be considered.
- The choice of protocol will depend on expected response of the patient.

References

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Thank You For Listening

