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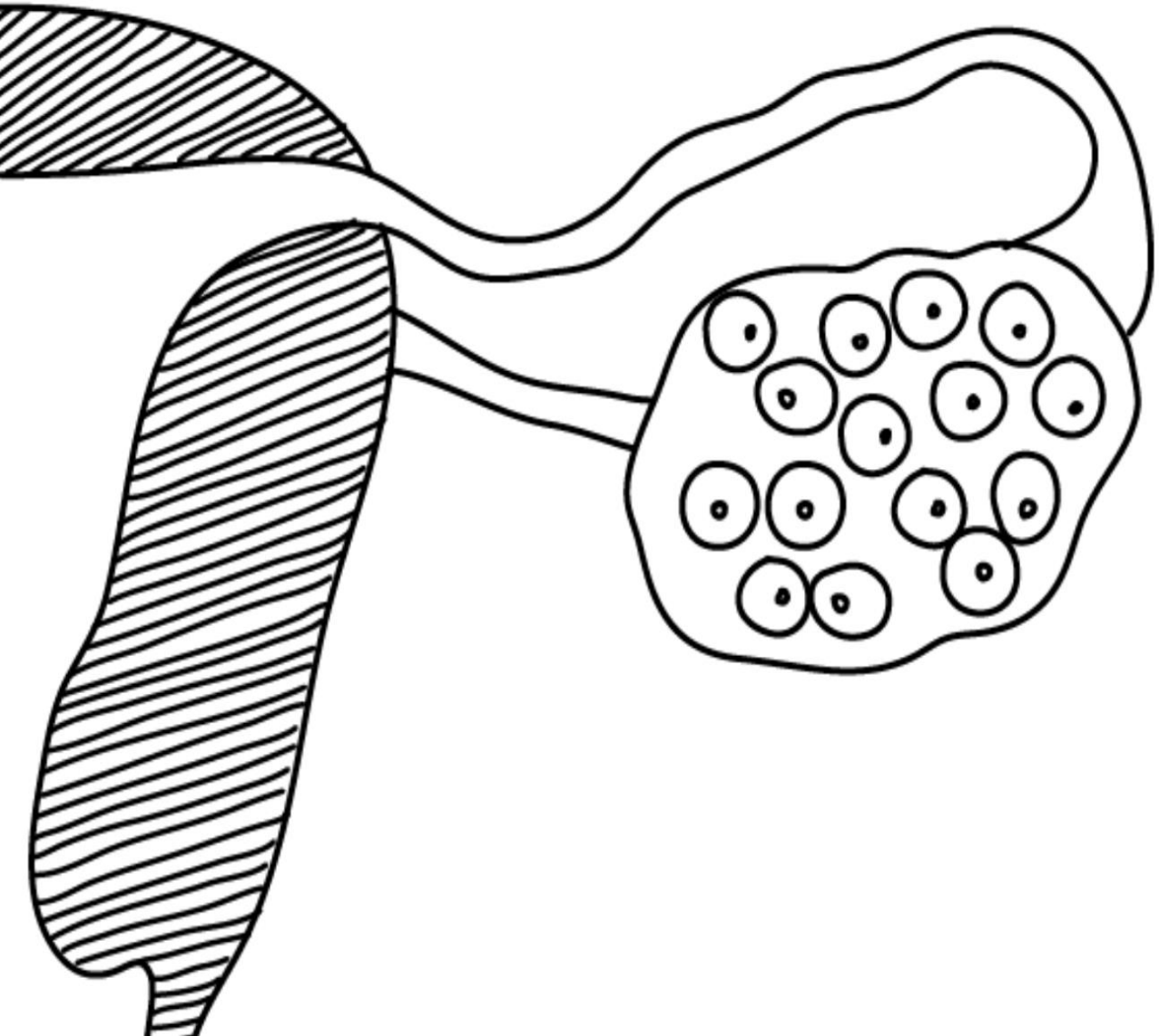

Ovarian Hyperstimulation Syndrome: still a problem?

Melissa Boccaccini

9/12/2019

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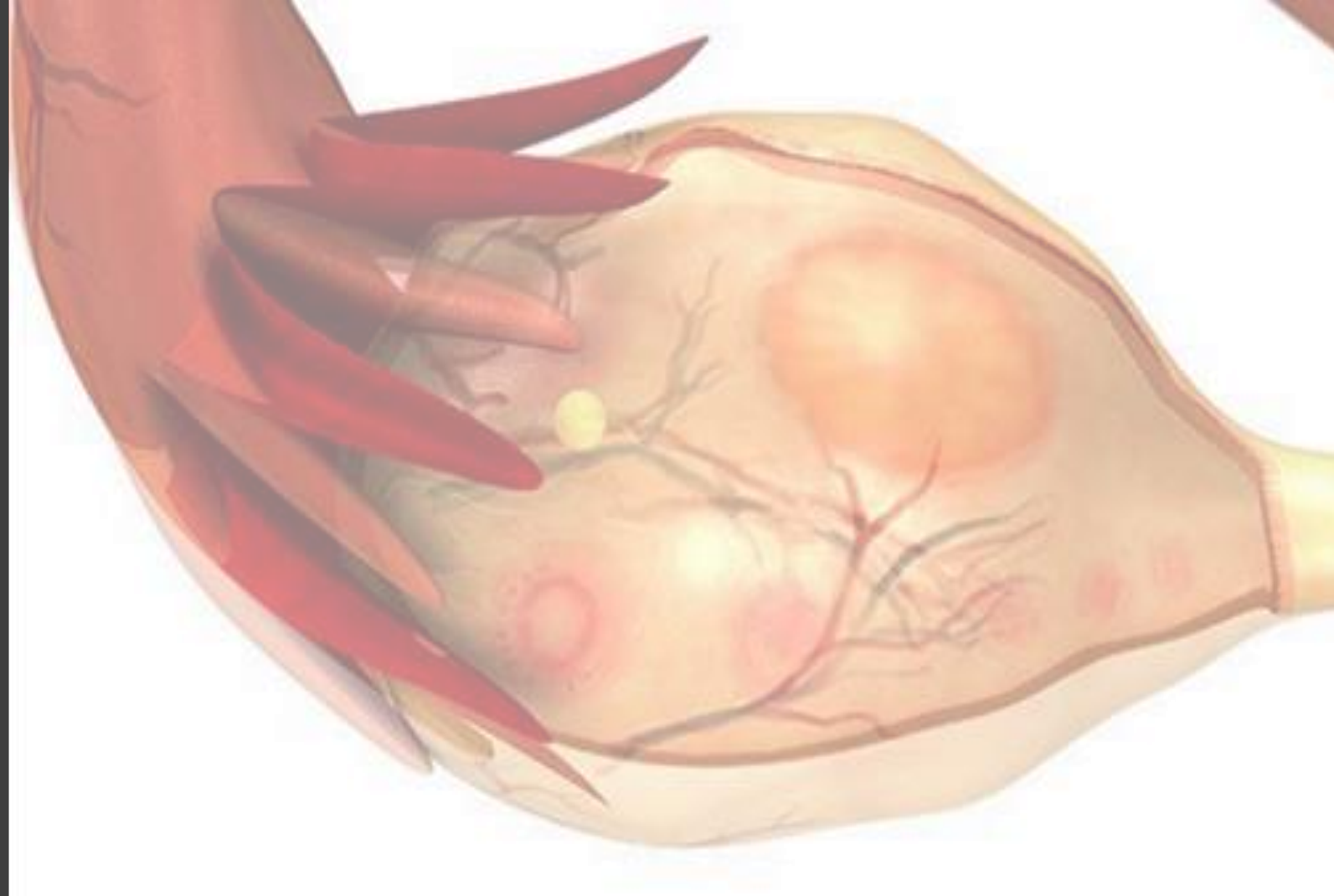

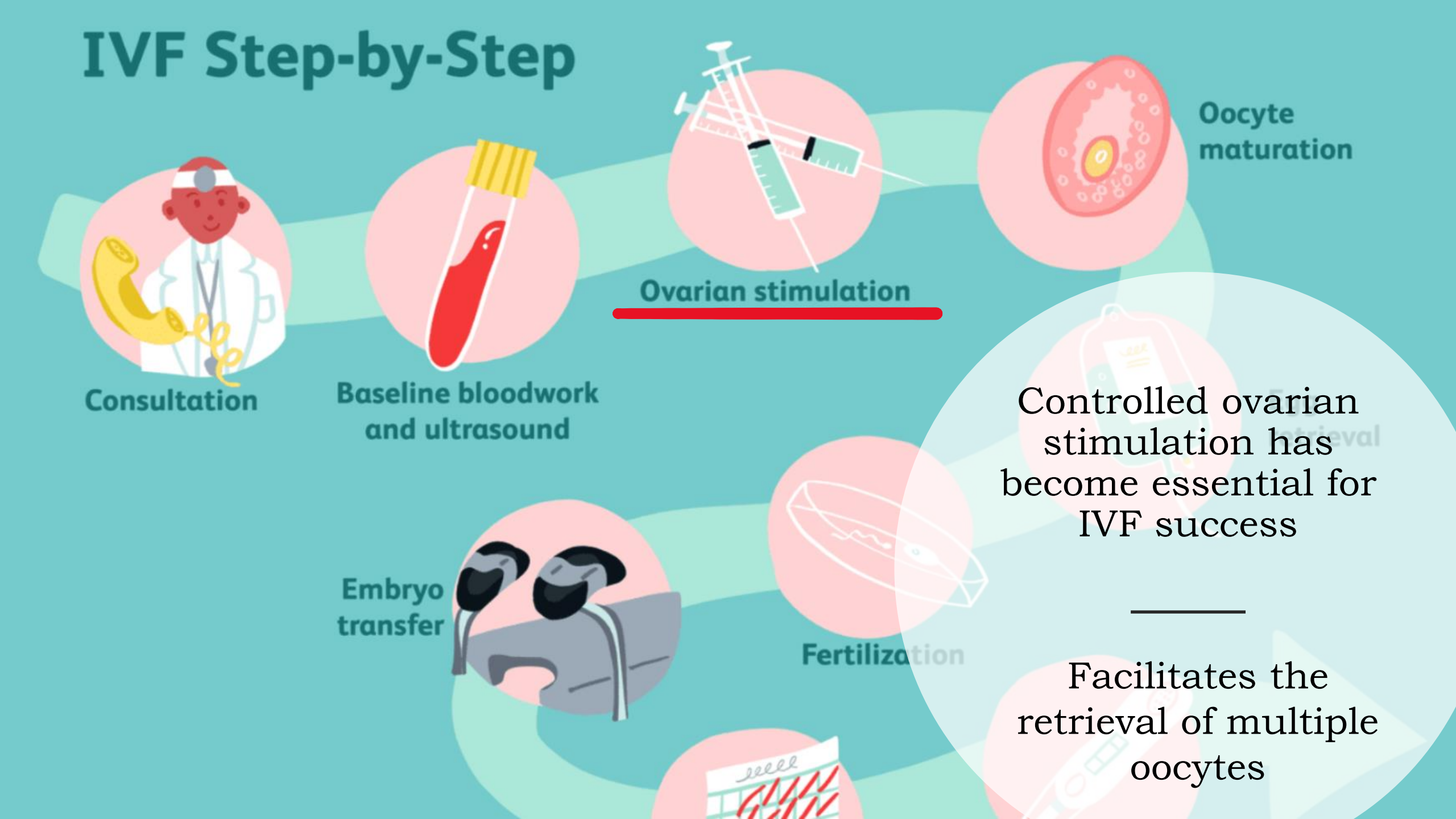

Controlled ovarian stimulation has become essential for IVF success

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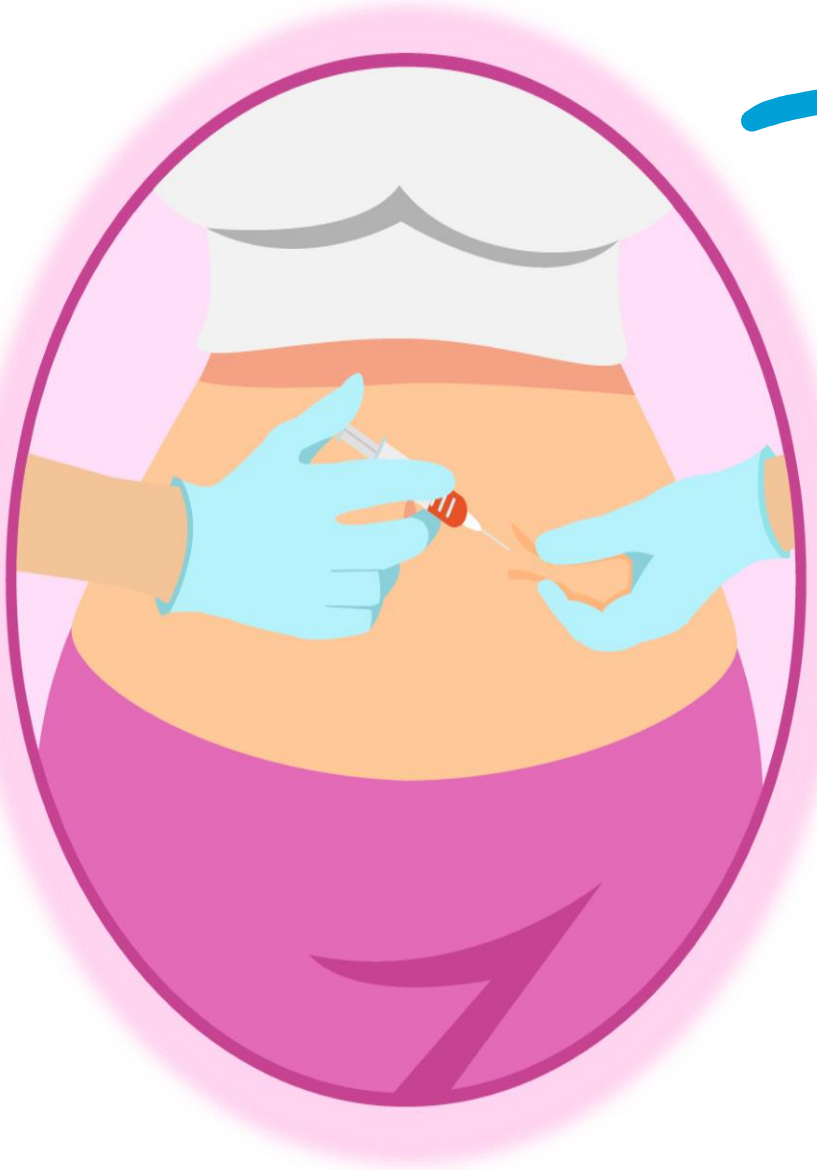
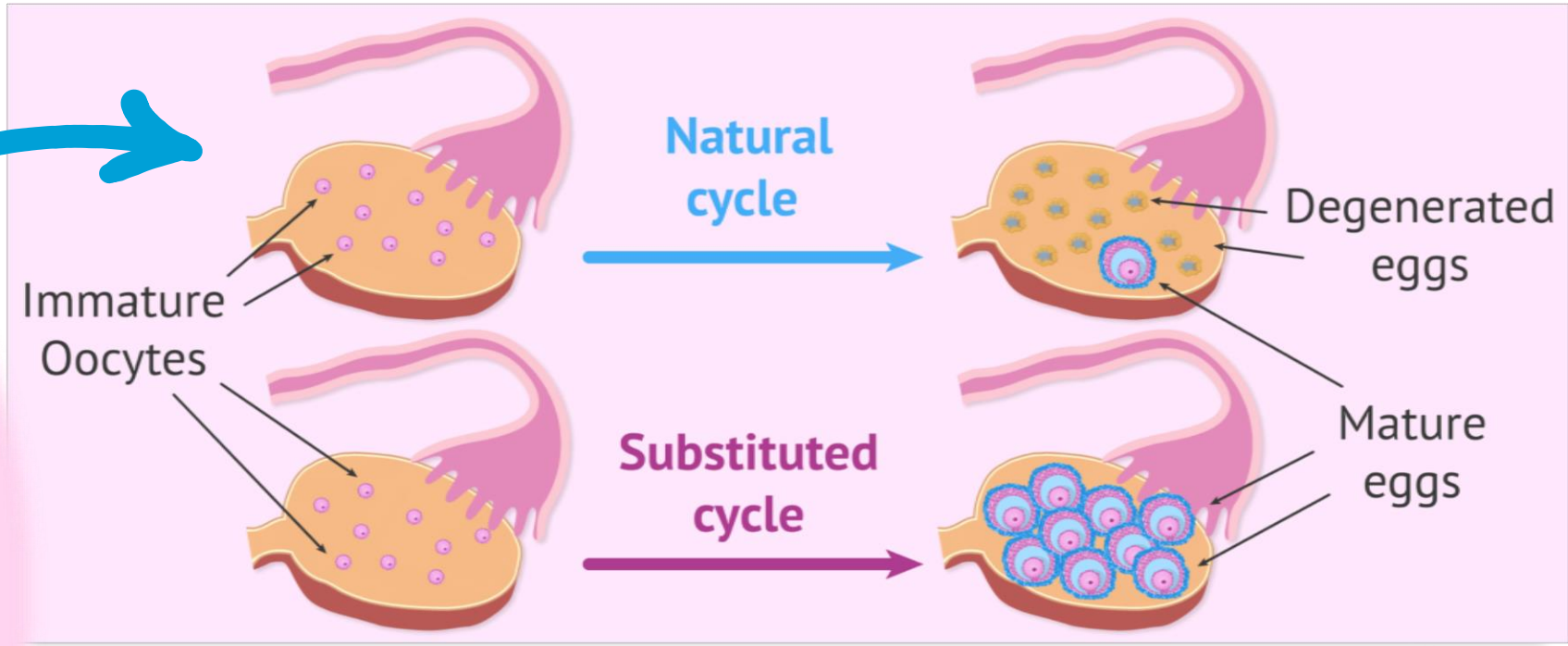
Facilitates the retrieval of multiple oocytes

Basics of COS:

Elevation of FSH levels over the normal threshold and for a much longer period of time





Response predictors:

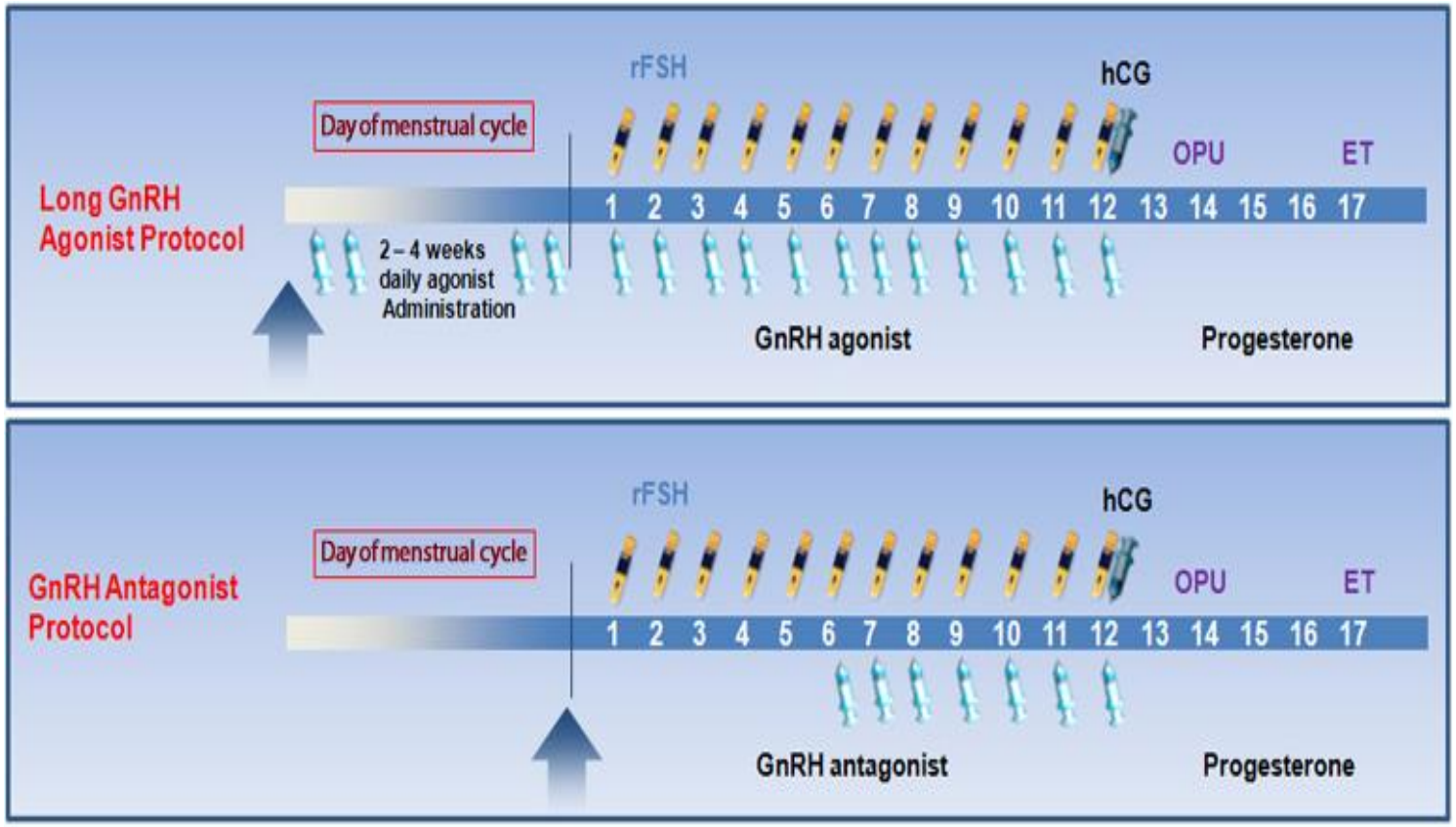
- Antral follicle count (AFC)
- Circulating AMH
- Maternal age
- Body mass index (BMI)
- Previous hyperstimulation experiences

Ovarian response to COS:

POOR

NORMAL

HIGH



Ovulation suppression

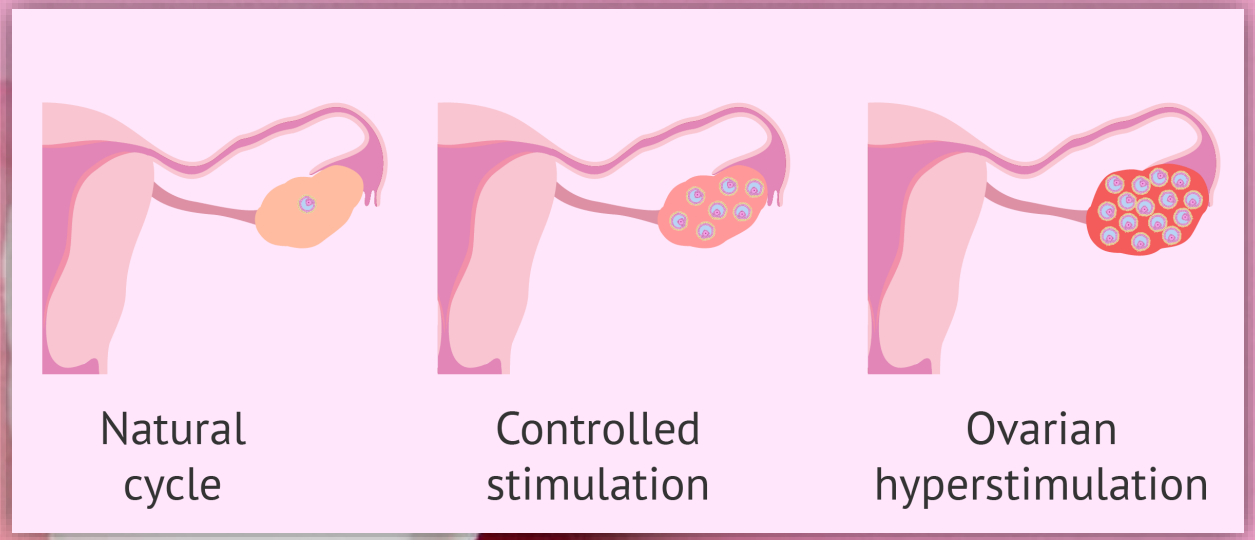
Mid-cycle LH surge can trigger ovulation too soon

↓

Use of agents that block the GnRH signaling towards the pituitary

Ovulation triggering

- LH-like exposure is provided mainly thourgh **human chorionic gonadotrophin** (hCG).
- **hCG is the most frequent aetiological factor in the development of OHSS:** serious iatrogenic complication of ovarian stimulation for assisted reproductive technologies.



Enlarged ovaries and increased number of stimulated follicles: **HYPER RESPONSIVENESS TO OVARIAN STIMULATION**

EARLY

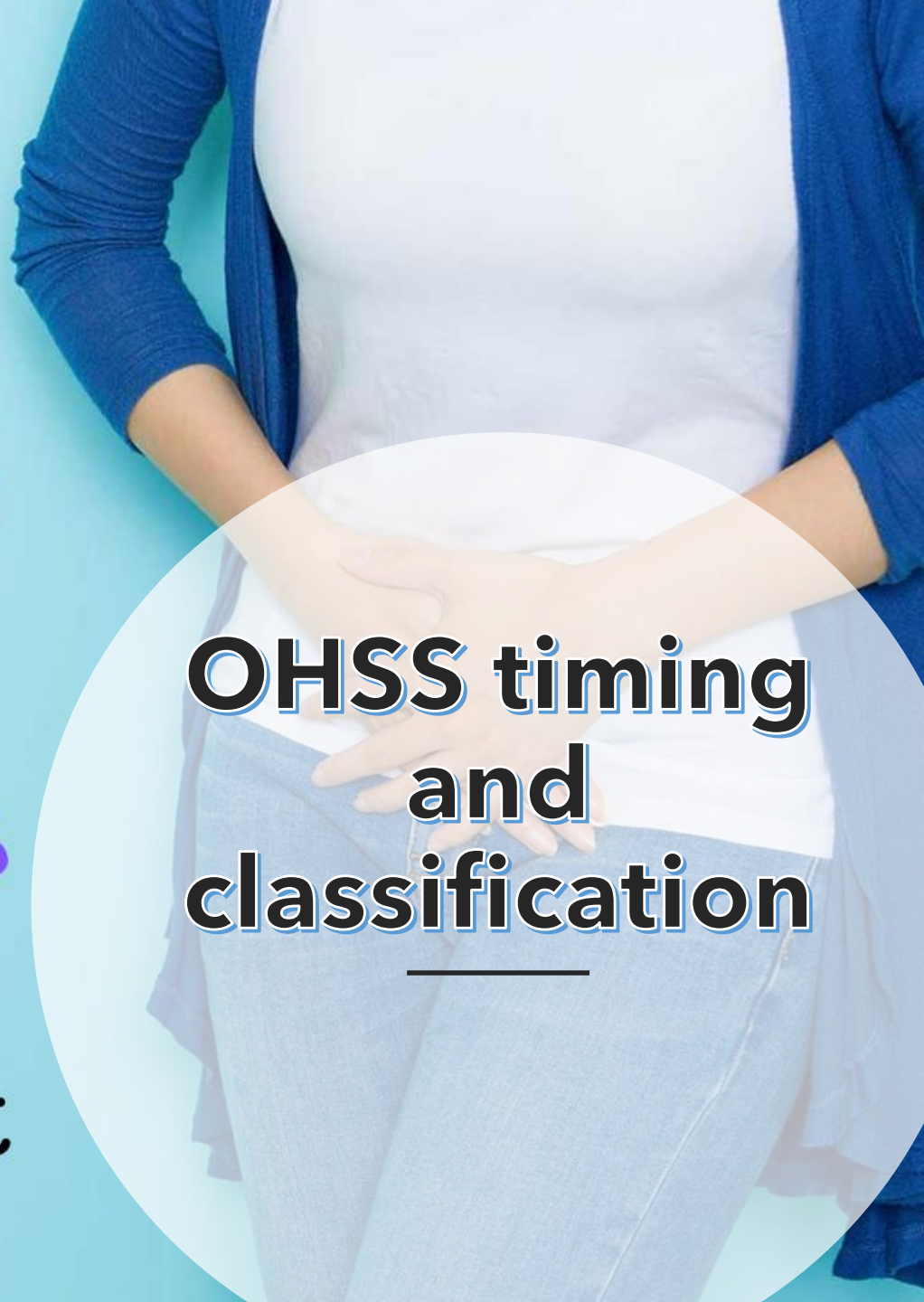
≤ 9 days
after hCG
administration

Caused by
EXOGENOUS
hCG

LATE

≥ 10 days
after hCG
administration

ENDOGENOUS
hCG after
pregnancy
establishment

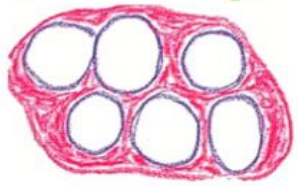


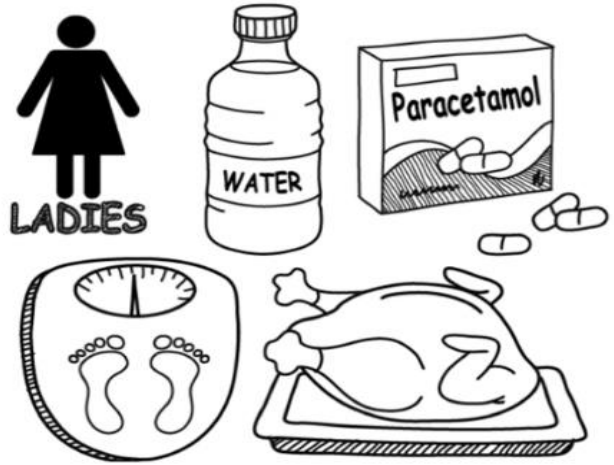
OHSS timing and classification

OHSS classification

MILD → 20-30% of IVF cycles →

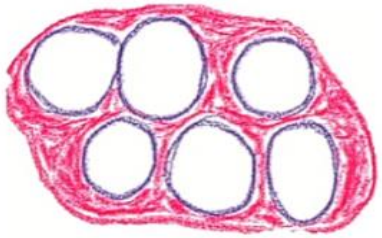
less than 8 cm





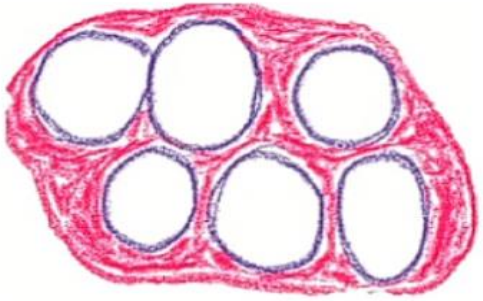
MODERATE 3-6%

8-12 cm



SEVERE 0.1-2%

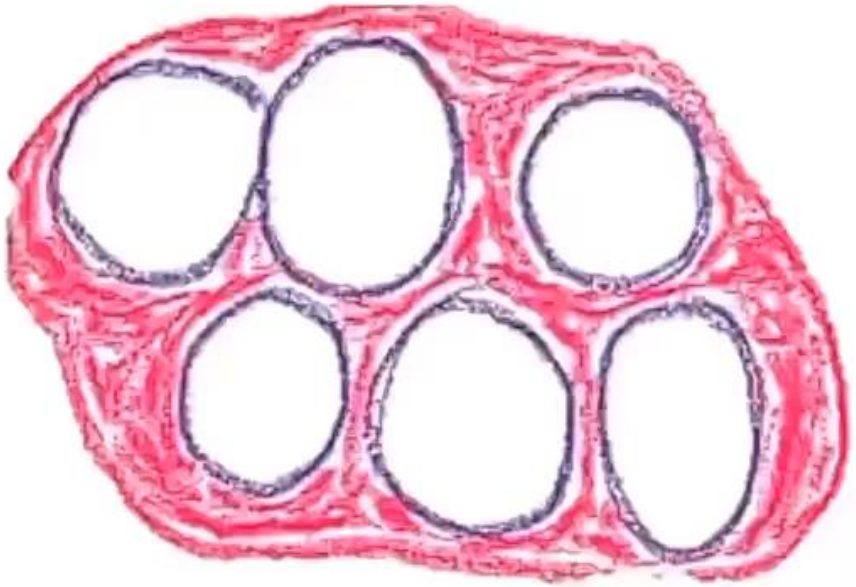
more than 12cm



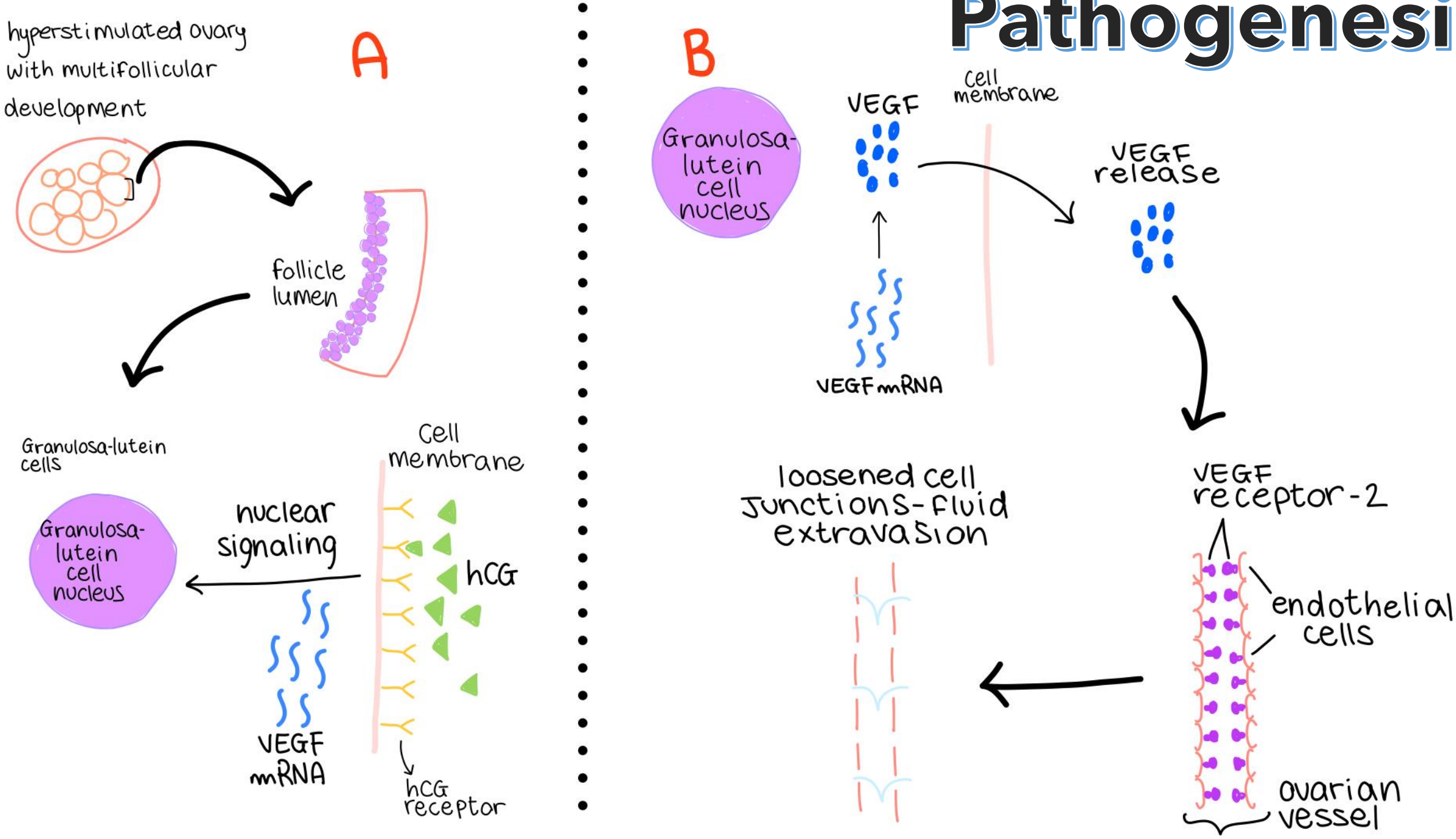
Category	Features
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually <8 cm†
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size usually 8–12 cm†
Severe OHSS	Clinical ascites (± hydrothorax) Oliguria (<300 ml/day or <30 ml/hour) Haematocrit >0.45 Hyponatraemia (sodium <135 mmol/l) Hypo-osmolality (osmolality <282 mOsm/kg) Hyperkalaemia (potassium >5 mmol/l) Hypoproteinaemia (serum albumin <35 g/l) Ovarian size usually >12 cm†
Critical OHSS	Tense ascites/large hydrothorax Haematocrit >0.55 White cell count >25,000/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome

Clinical manifestations

Pathogenesis



Pathogenesis

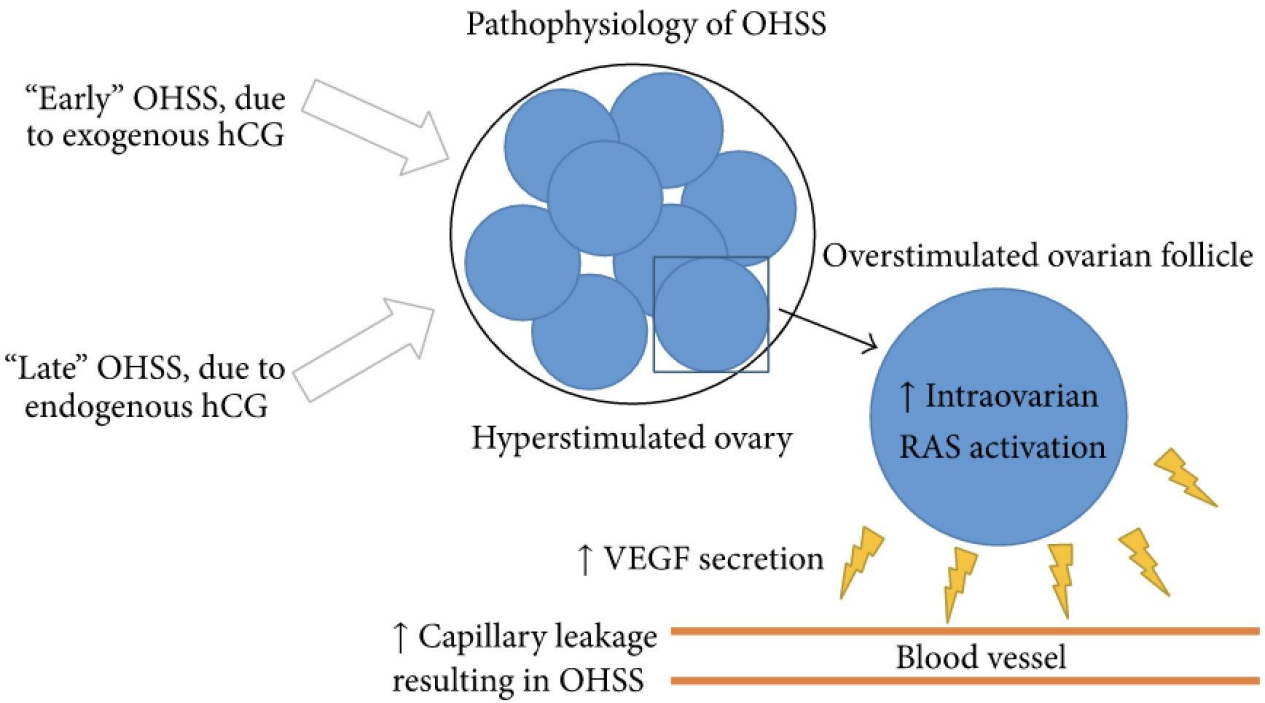


Estrogen-Induced Abnormally High Cystic Fibrosis Transmembrane Conductance Regulator Expression Results in Ovarian Hyperstimulation Syndrome

Louis Chukwuemeka Ajonuma, Lai Ling Tsang, Gui Hong Zhang, Connie Hau Yan Wong, Miu Ching Lau, Lok Sze Ho, Dewi Kenneth Rowlands, Chen Xi Zhou, Chuen Pei Ng, Jie Chen, Peng Hui Xu, Jin Xia Zhu, Yiu Wa Chung, and Hsiao Chang Chan

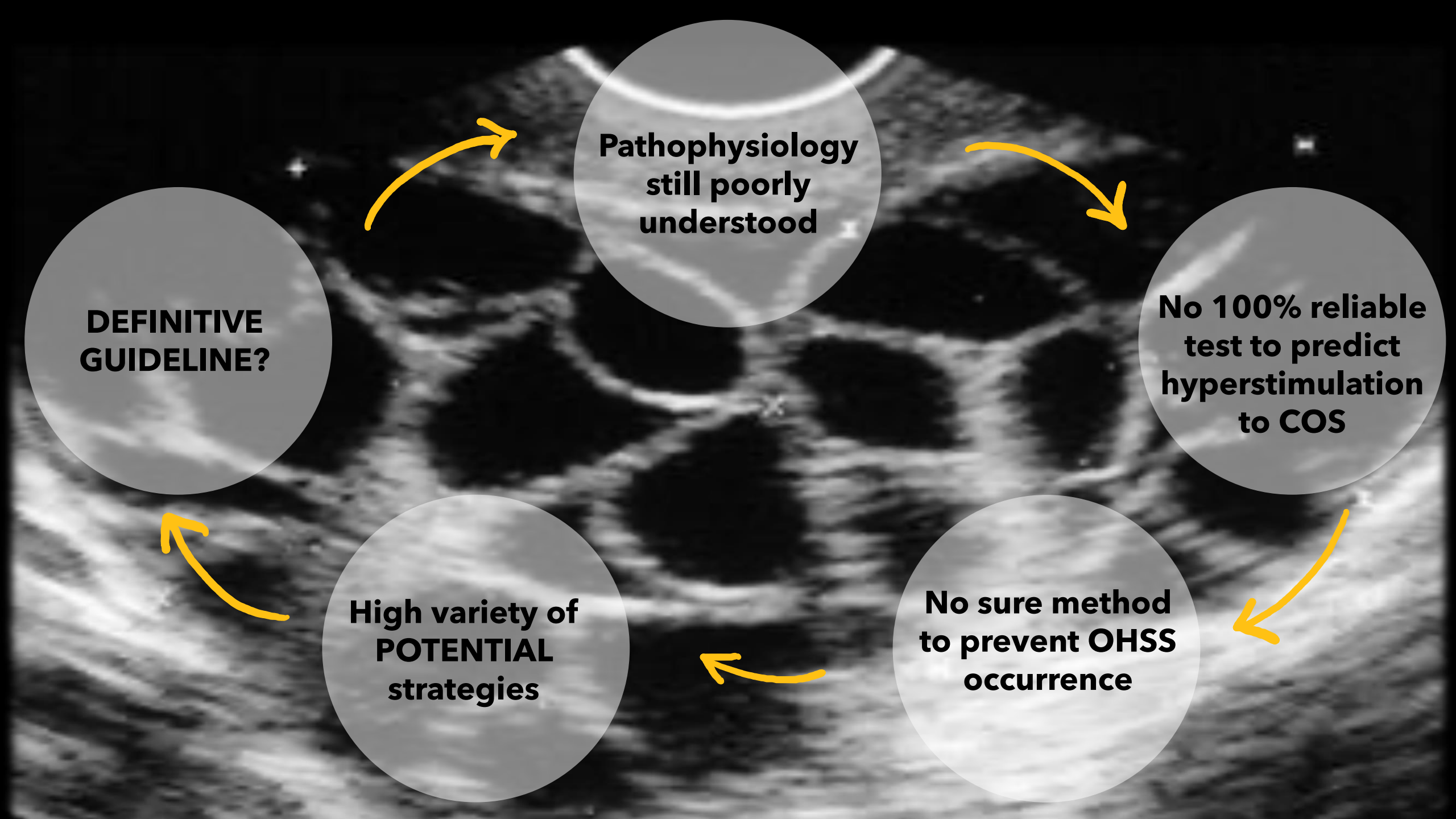
Epithelial Cell Biology Research Center, Department of Physiology, Faculty of Medicine, Chinese University of Hong Kong, Shatin, New Territory, Hong Kong

Ovarian hyperstimulation syndrome (OHSS) remains one of the most life-threatening and potentially fatal complications of assisted reproduction treatments, arising from excessive stimulation of the ovaries by exogenous gonadotropins administrated during *in vitro* fertilization procedures, which is characterized by massive fluid shift and accumulation in the peritoneal cavity and other organs, including the lungs and the reproductive tract. The pathogenesis of OHSS remains obscure, and no definitive treatments are currently available. Using RT-PCR, Western blot, and electrophysiological techniques we show that cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-activated chloride channel expressed in many epithelia, is involved in the pathogenesis of OHSS. Upon ovarian hyperstimulation, rats develop OHSS symptoms, with up-regulated CFTR expression and enhanced CFTR channel activity, which can also be mimicked by administration of estrogen, but not progesterone, alone in ovariectomized rats. Administration of progesterone that suppresses CFTR expression or antiserum against CFTR to OHSS animals results in alleviation of the symptoms. Furthermore, ovarian hyperstimulation does not induce detectable OHSS symptoms in CFTR mutant mice. These findings confirm a critical role of CFTR in the pathogenesis of OHSS and may provide grounds for better assisted reproduction treatment strategy to reduce the risk of OHSS and improve *in vitro* fertilization outcome. (*Molecular Endocrinology* 19: 3038–3044, 2005)



Pathogenesis

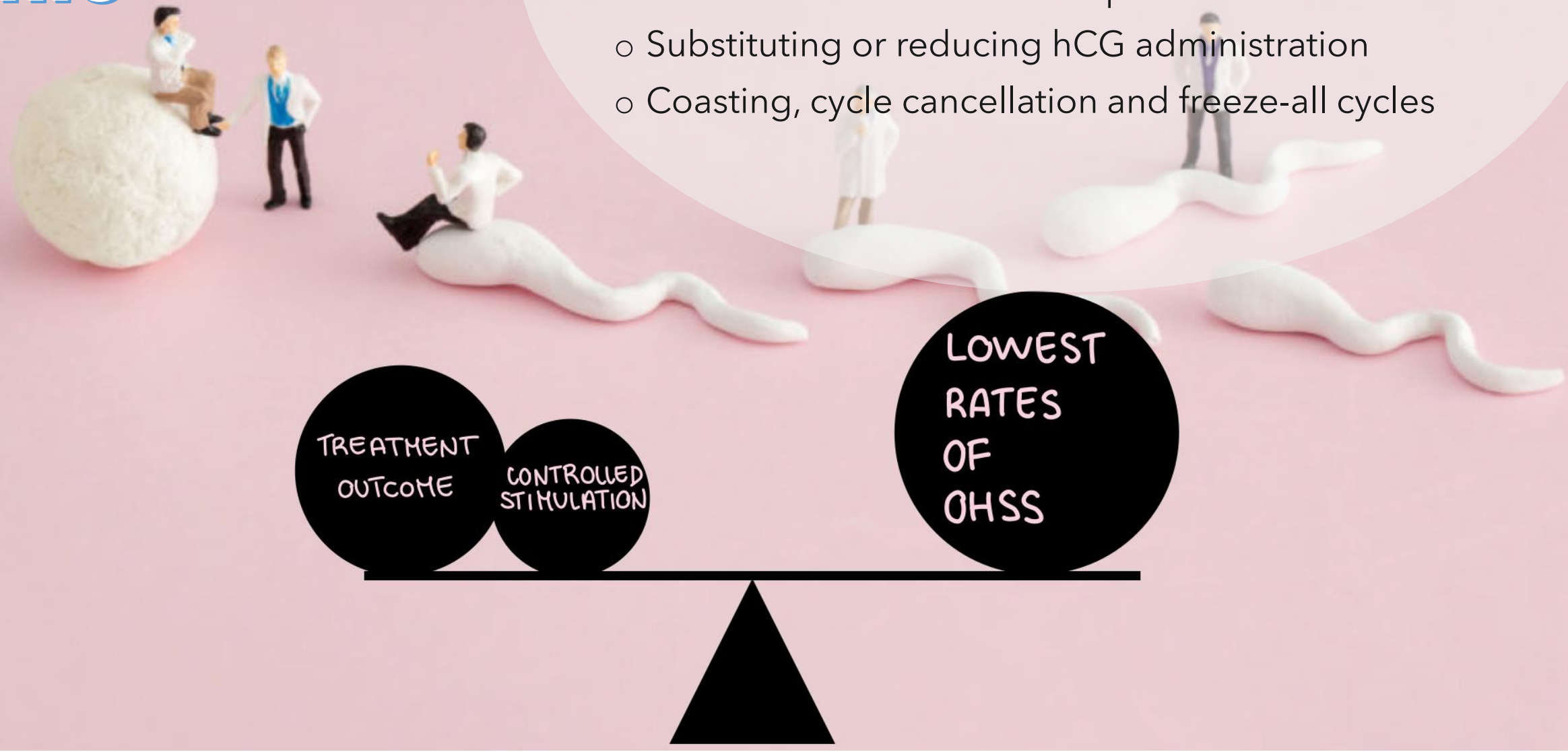
- Other vasoactive and inflammatory cytokines involved (Renin Angiotensin System, IL-6, IL-8, IL-2, TNF…)


Pathophysiology still poorly understood
No 100% reliable test to predict hyperstimulation to COS
No sure method to prevent OHSS occurrence
High variety of POTENTIAL strategies
DEFINITIVE GUIDELINE?

OHSS risk-free clinic

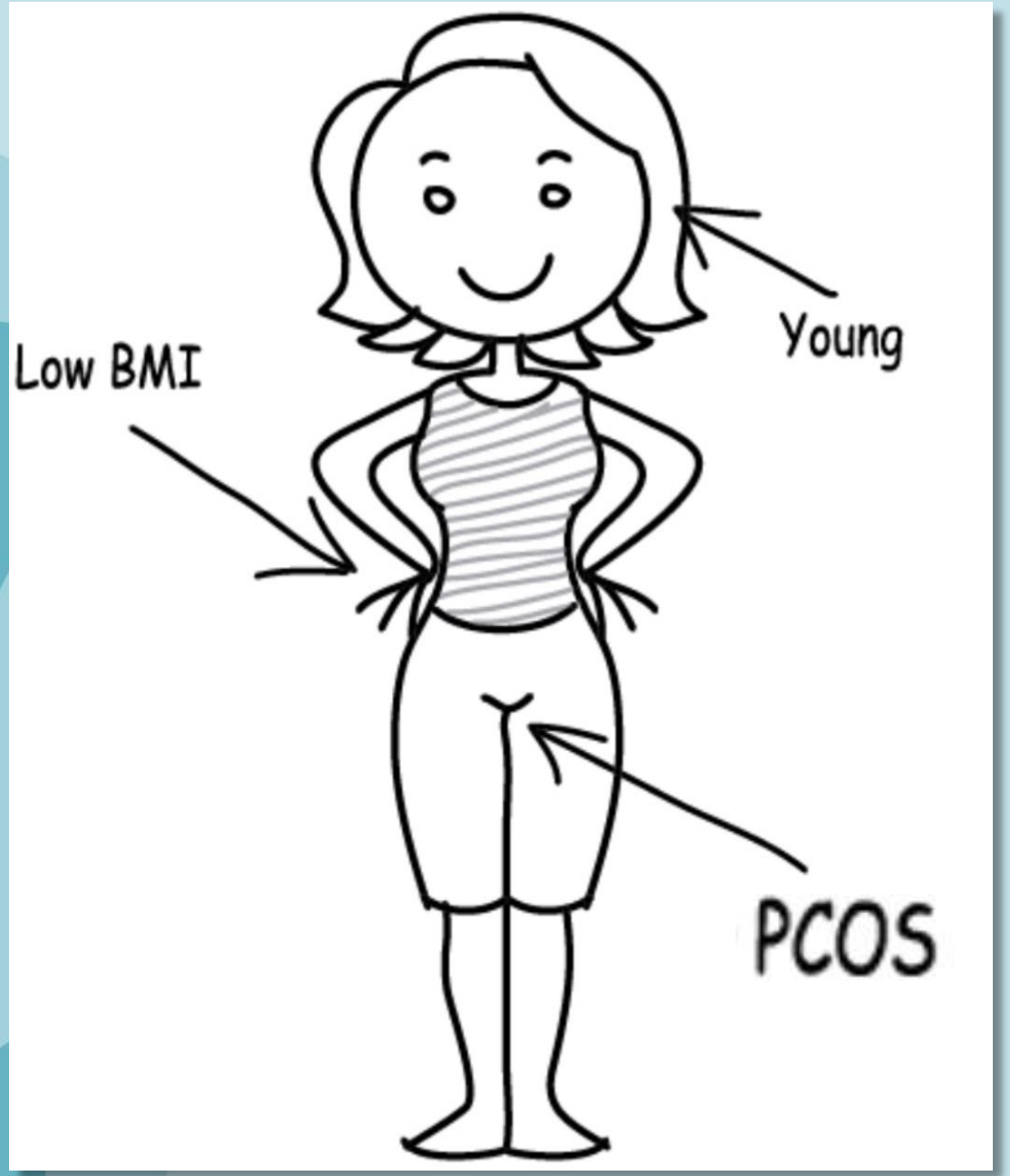
Interventions that aim to reduce OHSS occurrence:

- Identification of the high risk population and prediction of the possible ovarian response
- Tailored ovarian stimulation protocol
- Substituting or reducing hCG administration
- Coasting, cycle cancellation and freeze-all cycles



Who is at risk of moderate or severe OHSS?

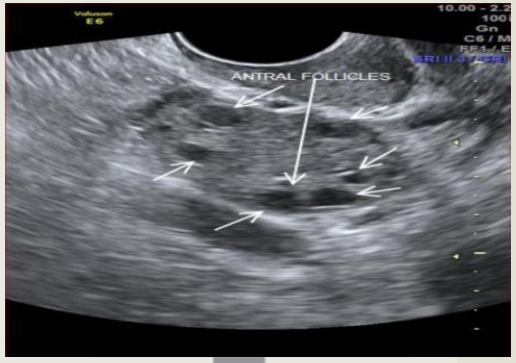
Assessment of **biomarkers** of ovarian reserve is highly recommanded in the pre-treatment routine for consequently planning an ovarian stimulation cycle based on the possible ovarian response.



What Does an Antral Follicle Count Test Do?

- Gives an idea of where fertility stands in relation to age
- Identifies primary ovarian insufficiency
- Helps diagnose polycystic ovarian syndrome
- Evaluates ovarian reserves

- Predicts OHSS?

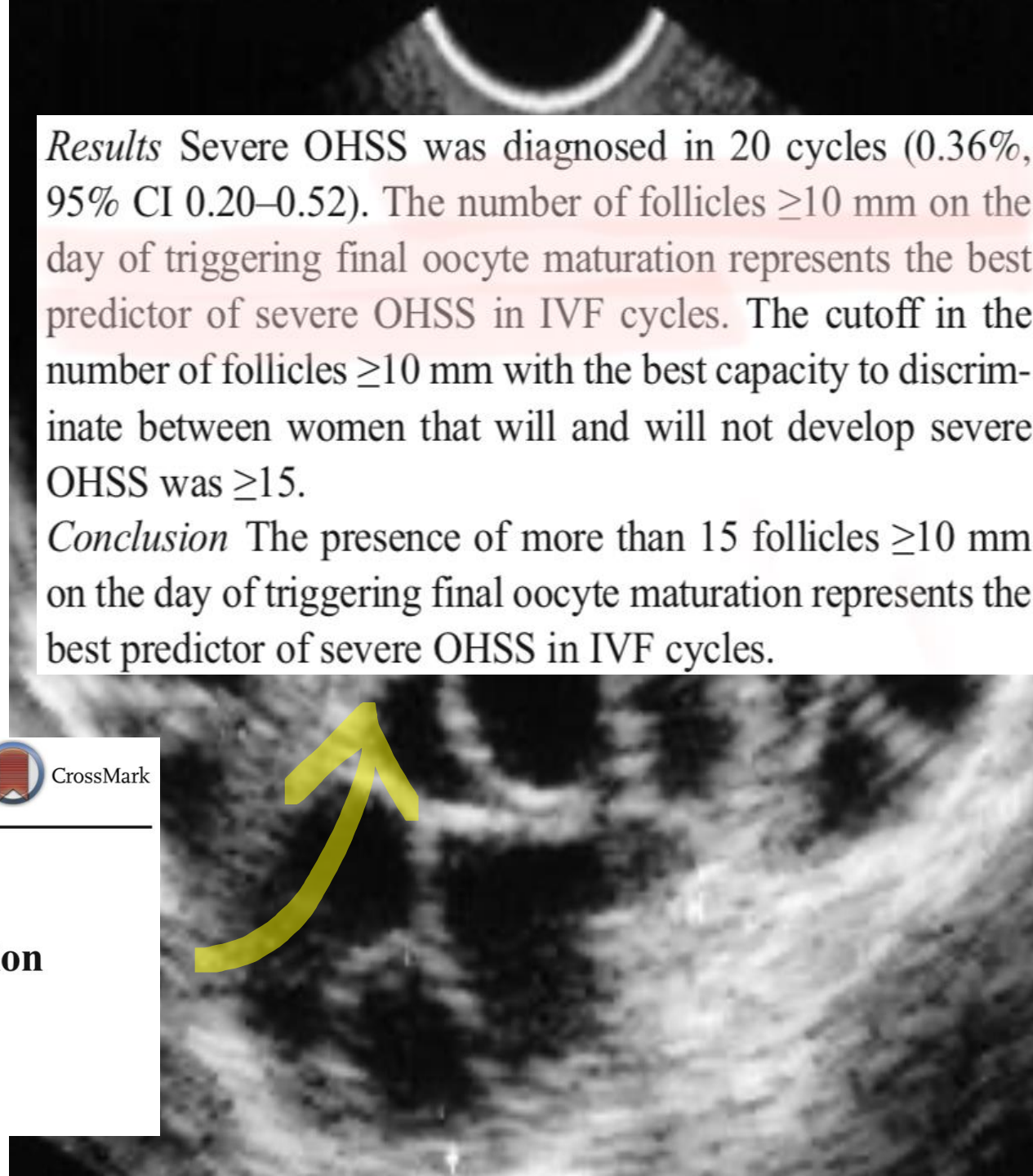


Parameters assessed before COS:

- **Basal serum FSH**: indirect marker of functional ovarian reserve (less accuracy).
- **Antral follicle count**: cohort of follicles capable of maturing during COS.
- **AMH**: higher values are related to a higher response to COS.

Parameters assessed during COS:

- **Estradiol levels**: marker of increased granulosa activity.
- **Number of larger follicles**: reflects the degree of ovarian stimulation.
- **Number of oocytes retrieved**



Results Severe OHSS was diagnosed in 20 cycles (0.36%, 95% CI 0.20–0.52). The number of follicles ≥10 mm on the day of triggering final oocyte maturation represents the best predictor of severe OHSS in IVF cycles. The cutoff in the number of follicles ≥10 mm with the best capacity to discriminate between women that will and will not develop severe OHSS was ≥15.

Conclusion The presence of more than 15 follicles ≥10 mm on the day of triggering final oocyte maturation represents the best predictor of severe OHSS in IVF cycles.

J Assist Reprod Genet (2017) 34:1341–1351
DOI 10.1007/s10815-017-0990-7

CrossMark

ASSISTED REPRODUCTION TECHNOLOGIES

What is the best predictor of severe ovarian hyperstimulation syndrome in IVF? A cohort study

Theoni B Tarlatzi[1] · Christos A Venetis[2] · Fabienne Devreker[1] · Yvon Englert[1] · Anne Delbaere[1]

Early follicular aspiration:

Follicle aspiration performed before or shortly hCG administration is believed to cause intrafollicular hemorrhage and a decline in some ovarian substances such as estradiol, progesterone and hCG: results too controversial and imprecise to draw any definitive conclusion.

PCO patient with:
-follicular antral count over 20
-several previous failed attempts
-previous OHSS

100 iu FSH were given for 7 days

When leading follicles are 14 mm HCG was given

hCG 5000 iu were given and oocytes retrived 36 hours later.
The oocyte retriveal gave 10 mature oocytes for IVF and many immature oocytes

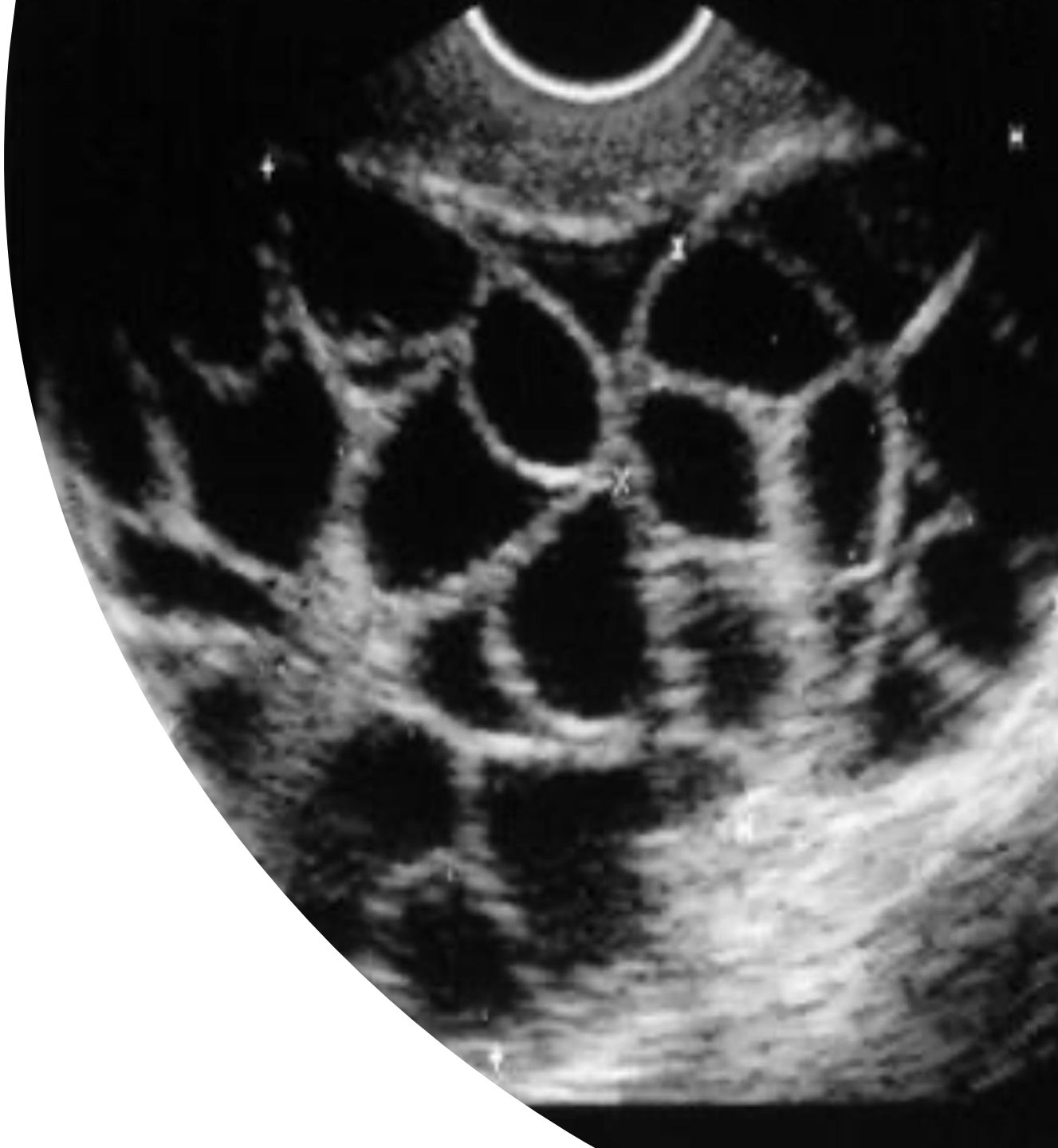
One 4 celle embryo was transferred back and 6 embryos were cryopreserved
14 day later a positive pregnancy test were seen and in week 7 a living feteus was observed

Other interventions:

- **Albumin or other plasma volume expanders**: binds and neutralize vascular permeability mediators. Administration is advised after oocyte retrieval when signs of early OHSS after hCG administration are encountered.

- **Cabergoline or other dopamine agonists**: Inhibits VEGF receptor-2. Use is advised daily starting from hCG administration or on oocyte retrieval day.

- **Metformin**: Decreases ovarian sensitivity to FSH, possibly ameliorating the response to COS.



Coasting

OHSS risk

- Discontinuation of gonadotrophin administration while maintaining GnRH agonist and post-poning hCG administration until serum estrogen levels fall into a more desirable concentration

WHEN AND FOR HOW LONG?

Coasting is not a universally accepted technique, and there is no consensus regarding the criteria used to start coasting, or the length of time before hCG administration. Coasting is generally used for 3–4 days; prolonging coasting beyond 4 days might cause a marked decrease in blood estradiol levels, leading to poor oocyte quality and decreased implantation and pregnancy rates[118].

Ultrasound Obstet Gynecol 2015; **45**: 377–393. *Nastri et al.*

Mild stimulation

Current evidence from RCTs.

Eight studies evaluated milder ovarian stimulation compared to the long-agonist protocol. Five studies used mild protocols with a GnRH antagonist and hCG triggering, one used clomiphene citrate and hMG, one used hMG only and one used less FSH in an agonist protocol .

REVIEW Open Access

The myths surrounding mild stimulation in vitro fertilization (IVF)

Raoul Orvieto[1,2*], Valeria Stella Vanni[1,3] and Norbert Gleicher[4,5,6,7]

Abstract

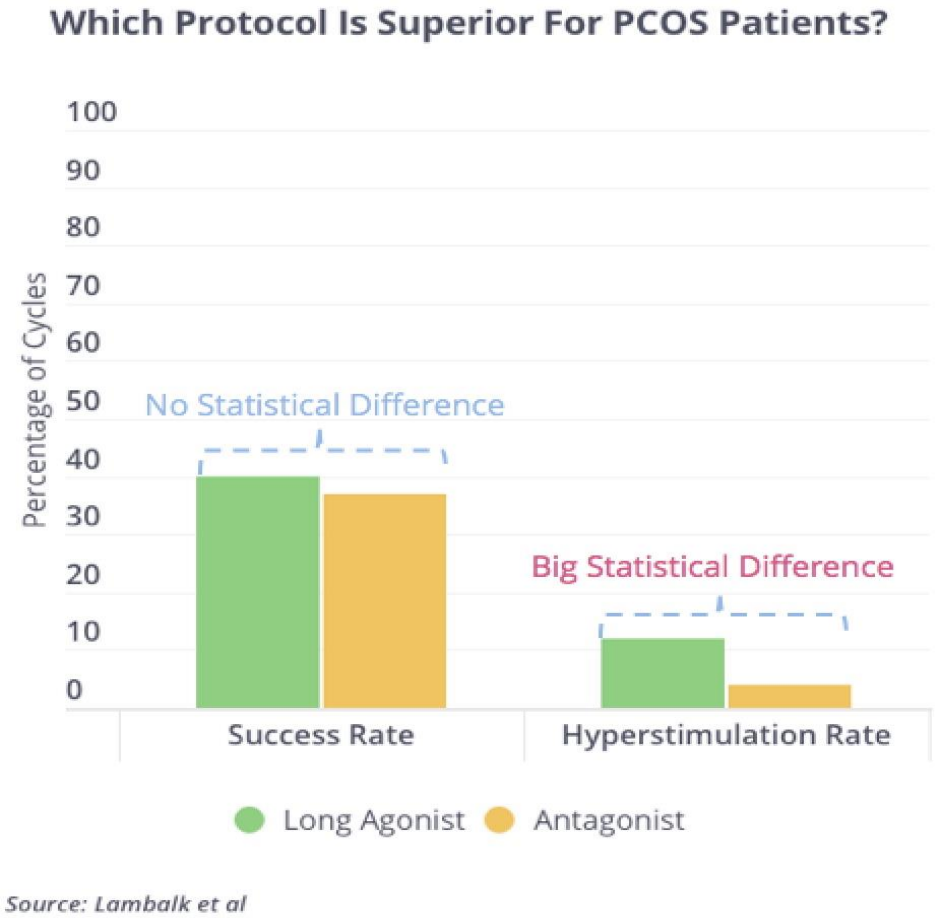
So-called mild controlled ovarian hyperstimulation (mCOH) has in recent years increased in popularity, claiming to be safer and more patient-friendly, while also improving in vitro fertilization (IVF) outcomes. We here challenge the International Society for Mild Approaches in Assisted Reproduction (ISMAAR) definition of mild stimulation, and especially address four fundamental issues, where our review found conventional COH (cCOH) advantageous over mCOH. They are: prevalence of severe ovarian hyperstimulation syndrome (OHSS), oocyte/embryo quality, pregnancy/live birth rates, and cost. We conclude that an objective review of the literature does not support the routine utilization of mCOH in assisted reproduction.

Keywords: Ovarian stimulation, Aneuploidy, Cost-effectiveness, Ovarian hyperstimulation syndrome (OHSS), In vitro fertilization (IVF), Pregnancy rates, Live birth rates

They all reported OHSS and clinical pregnancy rates; the average rate of OHSS in the control groups was 4.6%. We observed moderate-quality evidence that mild stimulation reduces OHSS without producing a clinically relevant difference in clinical pregnancy rate.

COMPARING PROTOCOLS:

	LONG AGONIST	ANTAGONIST
RATES OF SUCCESS	Comparable	Comparable
OHSS RISK	Highest	Lowest
DURATION	Longest	Shortest
BEST PATIENTS	History of premature ovulation	PCOS, high AMH or AFC, previous high egg count, African-American



Source: Lambalk et al

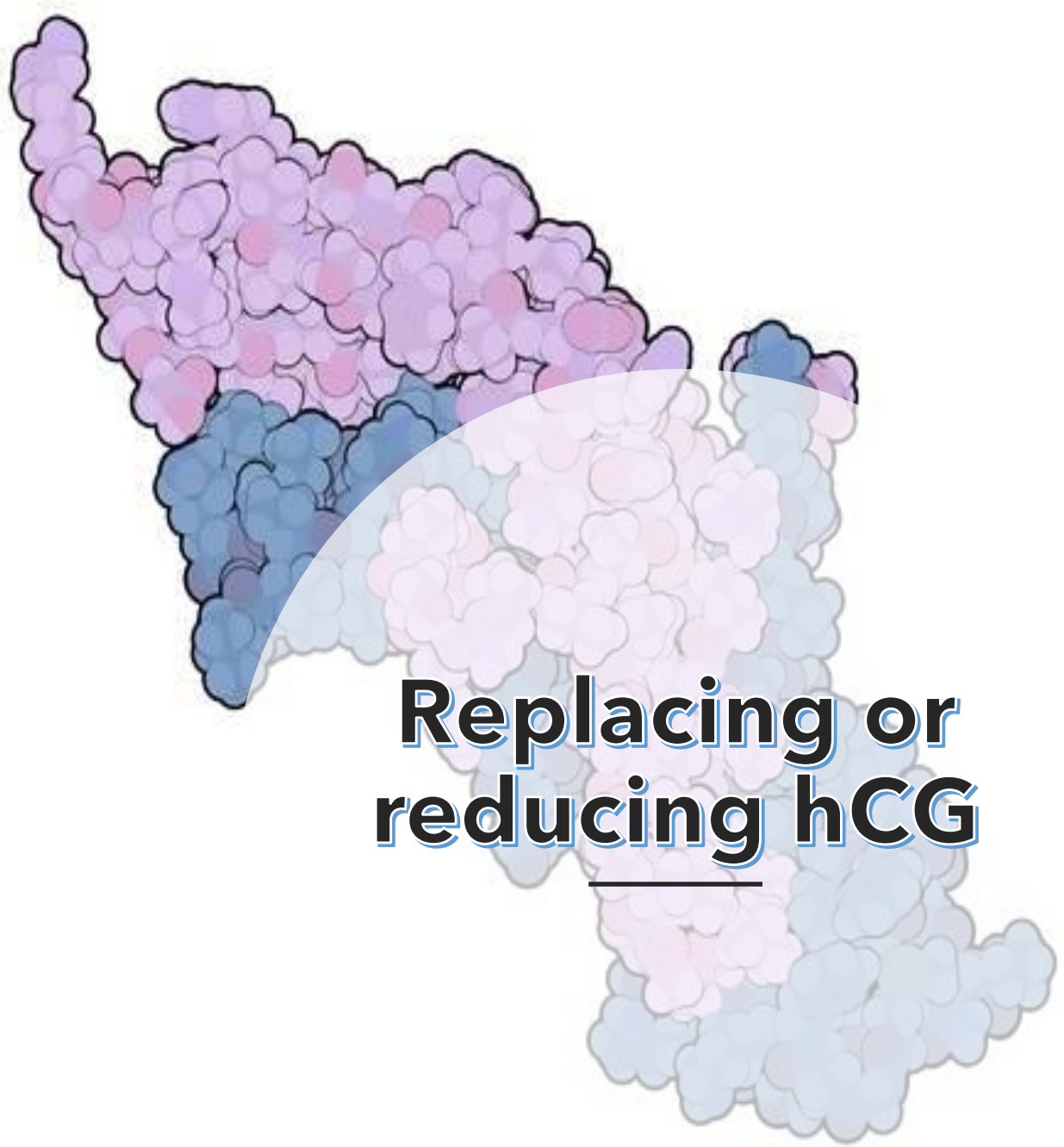
GnRH antagonists protocols

Eliminate OHSS

Eliminate hCG

Cycle cancellation

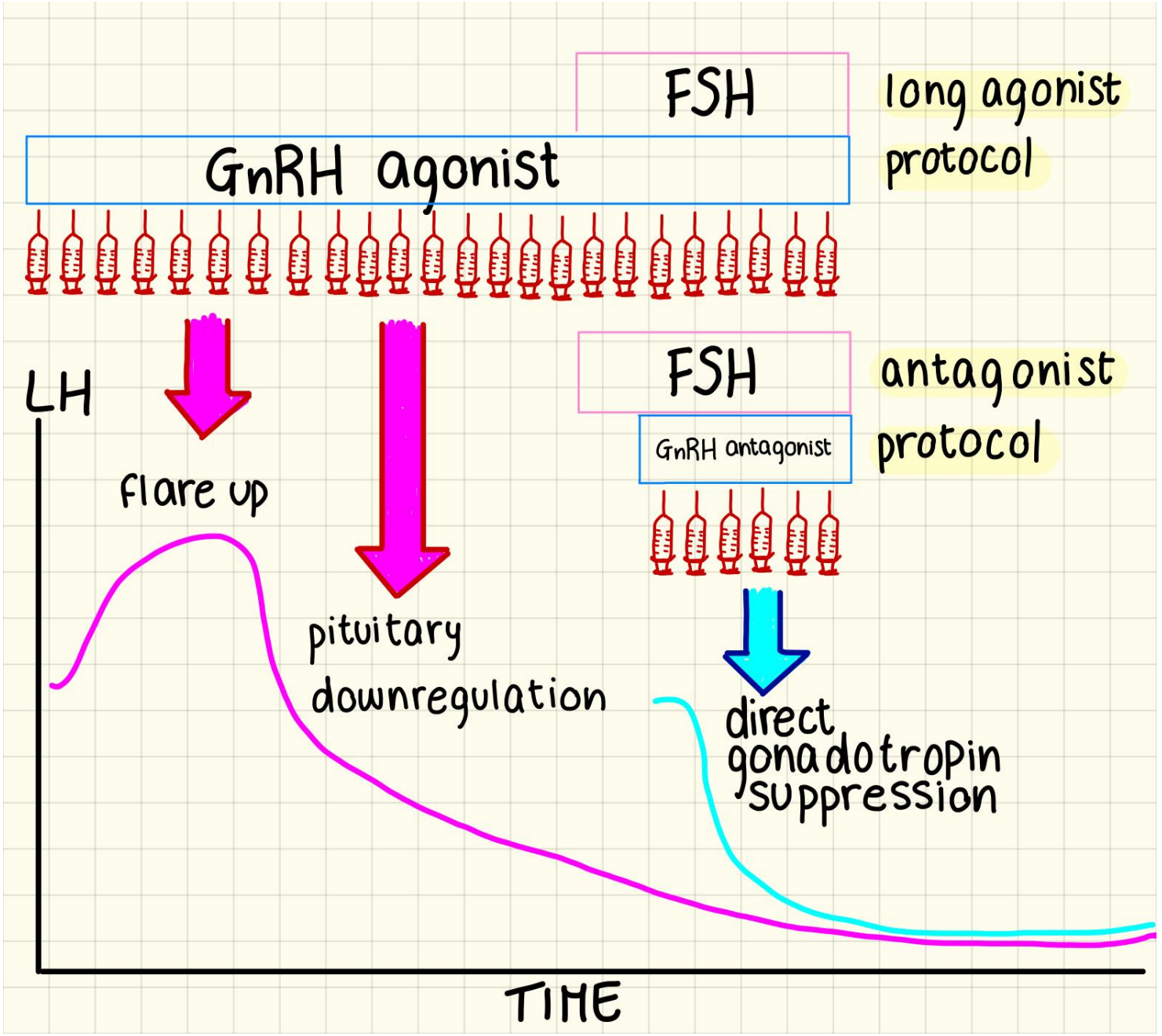
Replacement



Replacing or reducing hCG

GnRHan co-treatment and GnRHa trigger:

COMMON TOOL AIMING TO ELIMINATE SEVERE OHSS OCCURRENCE



FRESH EMBRYO TRANSFER

- GnRHa trigger induces early lutheolysis that requires lutheal support or administration of small doses of hGC to allow a fresh embryo transfer

OHSS

- GnRHa trigger can significantly reduce the incidence of OHSS
- A fresh embryo transfer can still cause late onset severe OHSS, especially if multiple embryos are transferred

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SCIENCE MOVING PEOPLE MOVING SCIENCE

OVARIAN STIMULATION FOR IVF/ICSI

Guideline of the European Society of Human Reproduction and Embryology

Recommendation

The GnRH antagonist protocol is recommended for PCOS women with regards to improved safety and equal efficacy.	Strong	⊕⊕◯◯

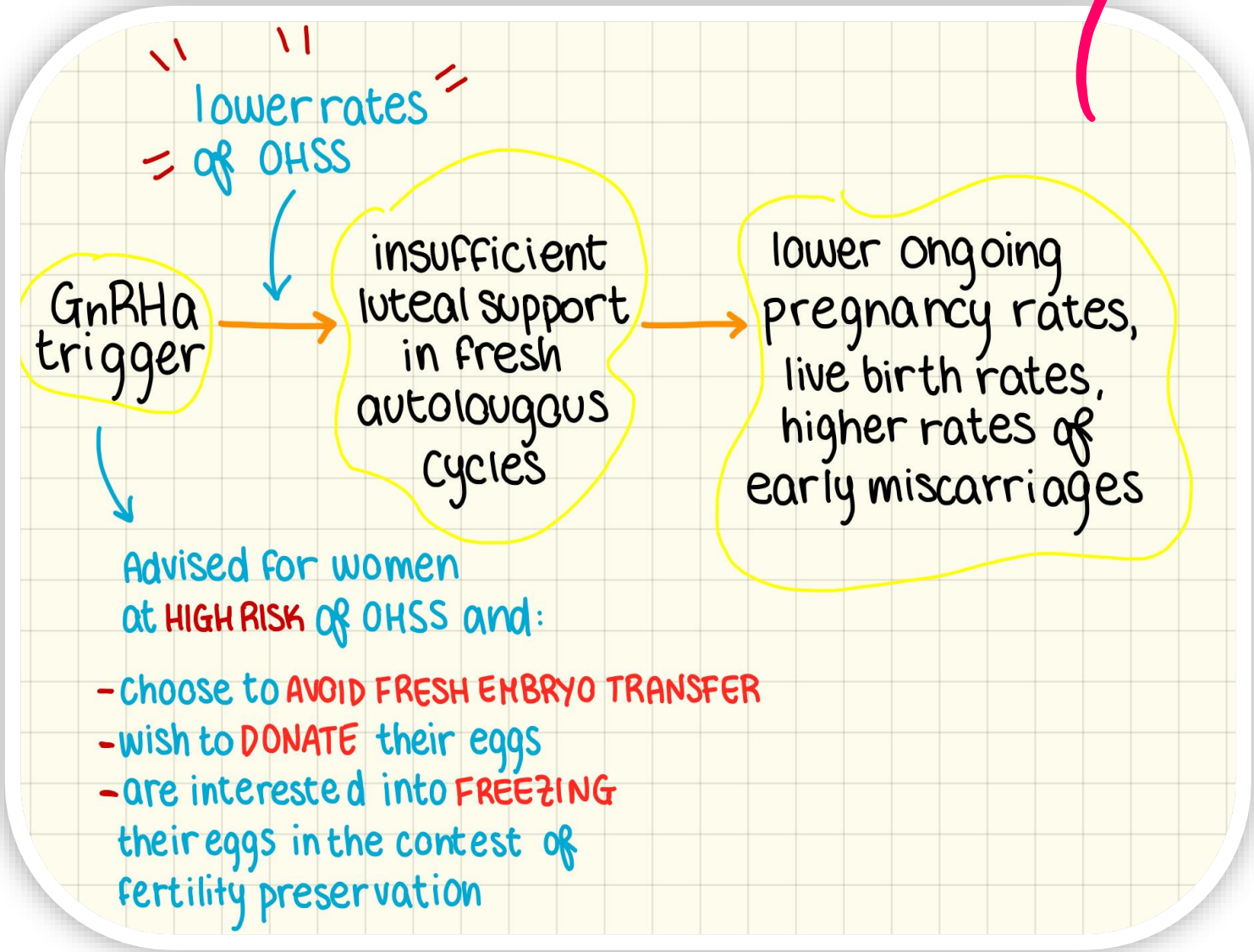
The GnRH antagonist protocol is recommended for predicted high responders with regards to improved safety and equal efficacy.	GPP

Justification

Evidence indicates that GnRH antagonist protocol is as effective as the GnRH agonist protocol, and significantly reduces the risk of OHSS in PCOS women.

Even though there is no specific evidence on predicted non-PCOS high responders or PCOM patients, consensus of the guideline group is that GnRH antagonist protocol should be recommended in these patient groups, as this protocol allows for the best options for prevention of the OHSS in these patient groups.

OHSS and fresh embryo transfer

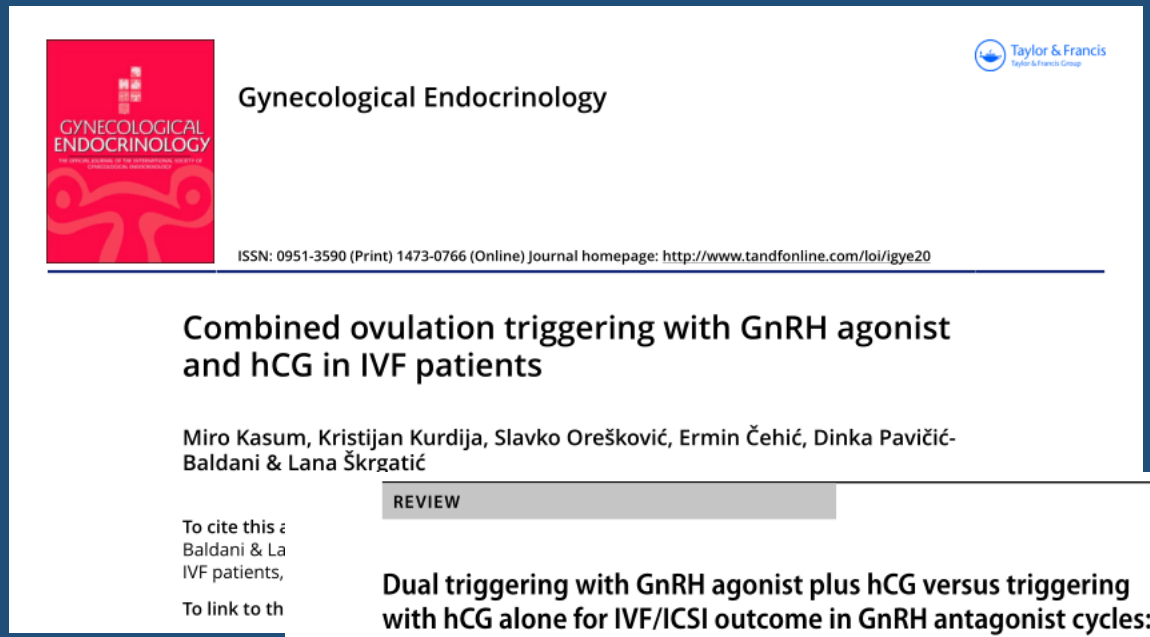


In the other cases:

- intensive luteal support with aggressive exogenous administration of estrogens and progesterone
- exogenous supplementation of a small dose of hCG on oocyte retrieval day or trigger day (DUAL TRIGGERING)

Dual triggering

- Corrects the luteal phase insufficiency
- Negates the advantages of removing the administration of exogenous hCG
- Possibility to tailor the hCG concentration to the observed ovarian response



Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

Combined ovulation triggering with GnRH agonist and hCG in IVF patients

Miro Kasum, Kristijan Kurdija, Slavko Orešković, Ermin Čehić, Dinka Pavičić-Baldani & Lana Škrgatić

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IVF patients,

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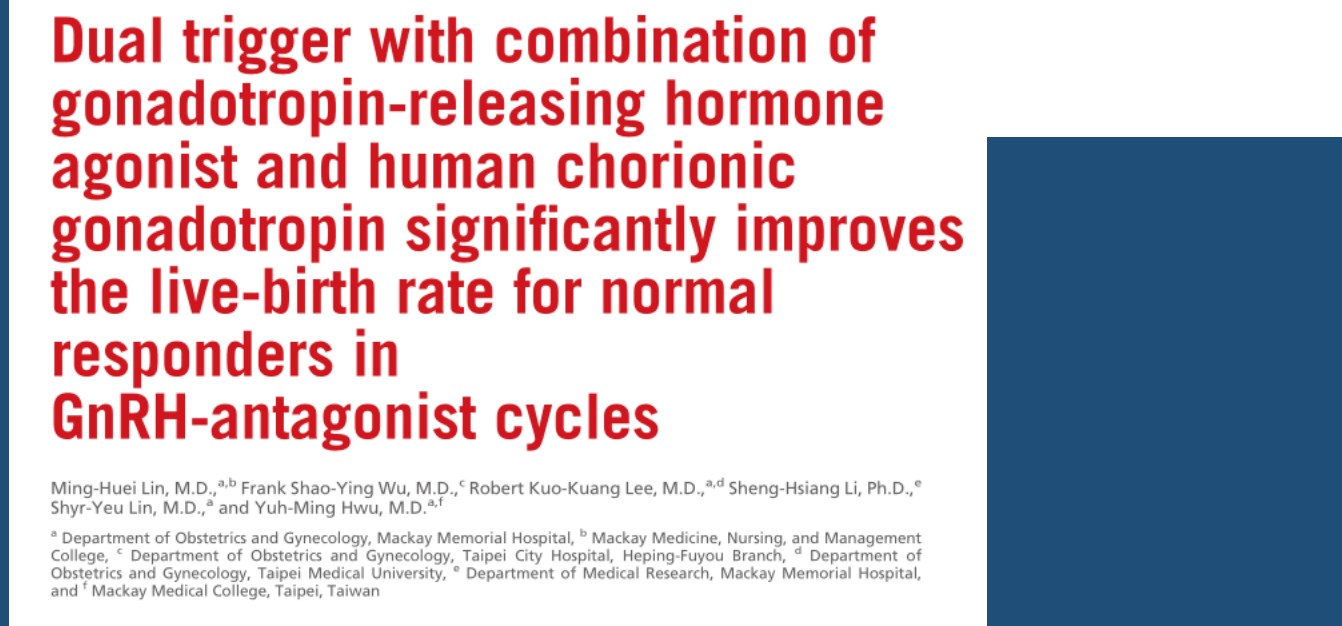
REVIEW

Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles: a systematic review and meta-analysis

Chi-Huang Chen[1,2] · Chii-Ruey Tzeng[1,2] · Peng-Hui Wang[3,4] · Wei-Min Liu[1,2] · Heng-Yu Chang[5,6] · Huang-Hui Chen[1] ·

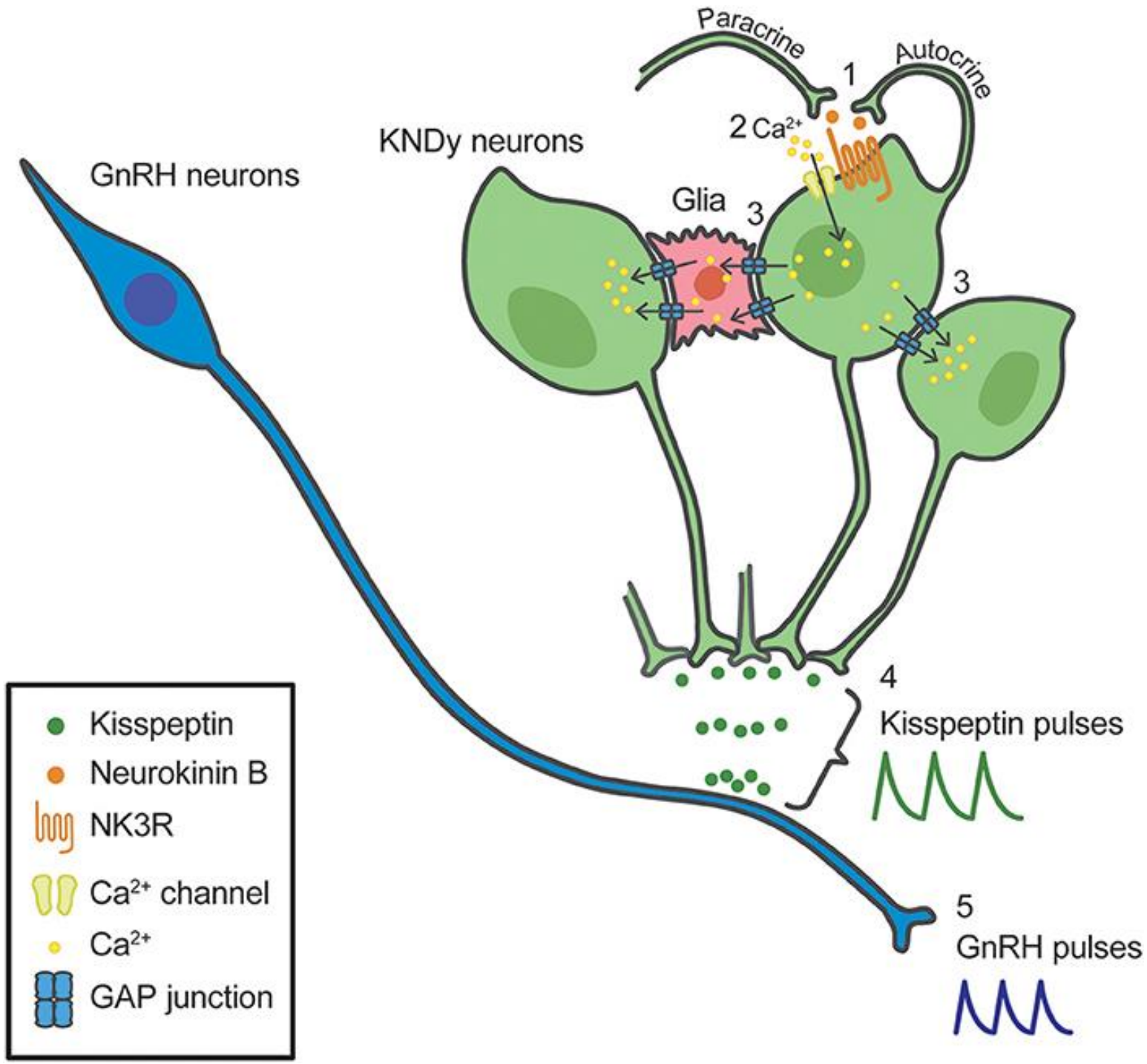


Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles

Ming-Huei Lin, M.D.,[a,b] Frank Shao-Ying Wu, M.D.,[c] Robert Kuo-Kuang Lee, M.D.,[a,d] Sheng-Hsiang Li, Ph.D.,[e] Shyr-Yeu Lin, M.D.,[a] and Yuh-Ming Hwu, M.D.[a,f]

[a] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, [b] Mackay Medicine, Nursing, and Management College, [c] Department of Obstetrics and Gynecology, Taipei City Hospital, Heping-Fuyou Branch, [d] Department of Obstetrics and Gynecology, Taipei Medical University, [e] Department of Medical Research, Mackay Memorial Hospital, and [f] Mackay Medical College, Taipei, Taiwan

Kisspeptin trigger?



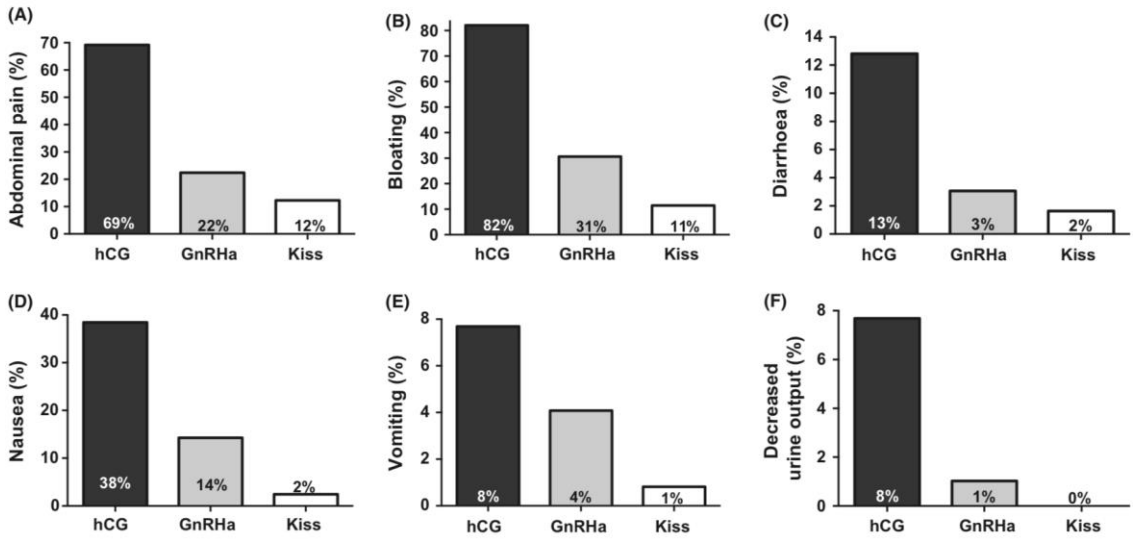


TABLE 2 Rates of early OHSS using different triggers

N	Normal	Mild OHSS	Moderate OHSS	Severe OHSS	Odds ratio of mild-severe OHSS (95% CI)	Odds ratio of moderate-severe OHSS (95% CI)
hCG (n = 40)	7 (18%)	18 (45%)	9 (23%)	6 (15.0%)	33.6 (12.6-89.5) $P < .0001$	80.7[a] (10.2-637.5) $P < .0001$
GnRHa (n = 99)	66 (67%)	30 (30%)	3 (3%)	0 (0%)	3.6 (1.8-7.1) $P < .0001$	5.1[a] (0.6-46.3) $P = .15$
Kisspeptin (n = 122)	107 (88%)	15 (12%)	0 (0%)	0 (0%)	-	-

Received: 24 January 2018 | Revised: 24 January 2018 | Accepted: 11 February 2018
DOI: 10.1111/cen.13569

ORIGINAL ARTICLE

WILEY

Clinical parameters of ovarian hyperstimulation syndrome following different hormonal triggers of oocyte maturation in IVF treatment

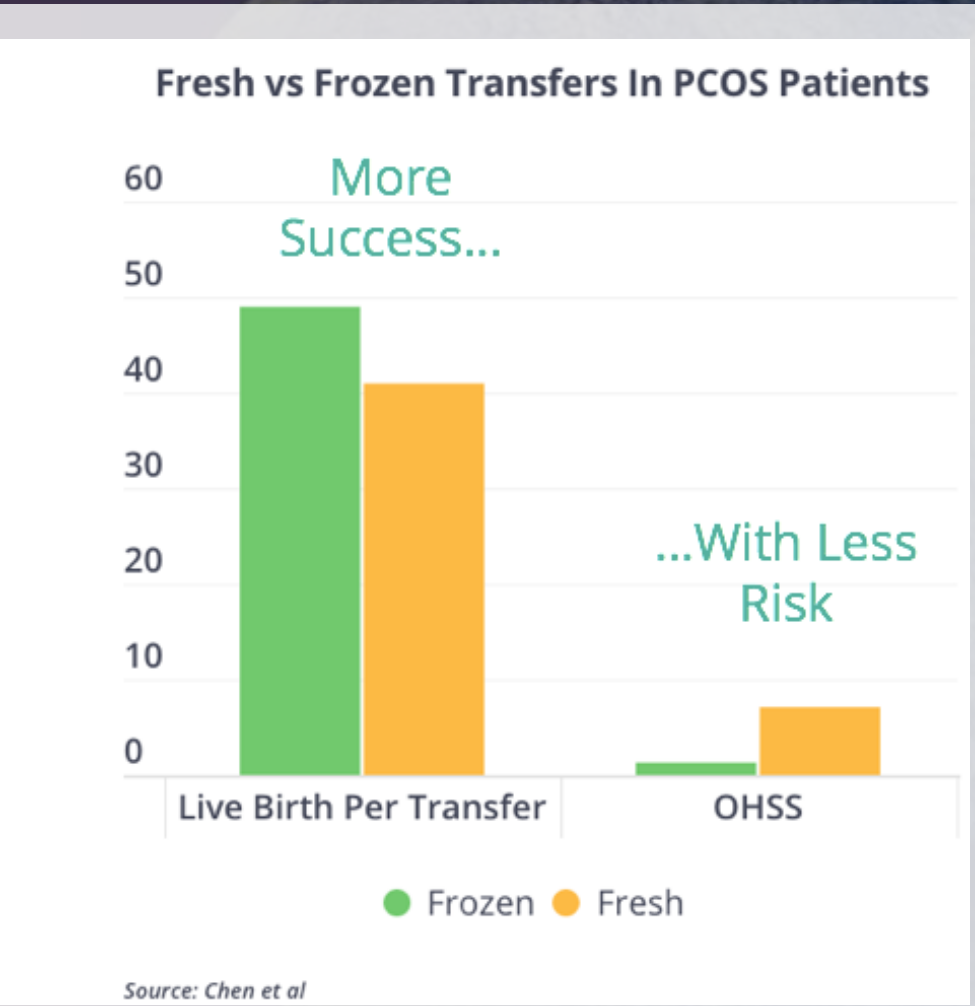
A. Abbara[1] | R. Islam[2] | S.A. Clarke[1] | L. Jeffers[1] | G. Christopoulos[2] | A.N. Comninos[1] | R. Salim[2] | S.A. Lavery[2] | T.N.L. Vuong[3,4] | P. Humaidan[5] | T.W. Kelsey[6] | G.H. Trew[2] | W.S. Dhillo[1]

Different mechanisms of action:

-hCG acts directly on the LH receptor, in the ovary, has an excessive duration of action
-GnRHa induce the release of gonadotropins and have shorter duration of action
-kisspeptin induces the release of GnRH directly from the hypothalamus.
OVARIAN ACTION: reduces the levels of VGEF

Segmentation of the cycle: cryopreservation

- Alternative to overcome the luteal phase insufficiency: **INCREASES THE PREGNANCY RATES**
- Prevents pregnancy in women that show signs of early OHSS also limiting the possibility of developing late onset OHSS.



Freeze-all cycles

1. GnRH antagonist protocol
2. GnRH agonist trigger
3. Cryopreservation of all embryos (or oocytes)
4. Frozen-thawed embryo transfer in a subsequent unstimulated cycle

ERASE THE RISK OF OHSS?

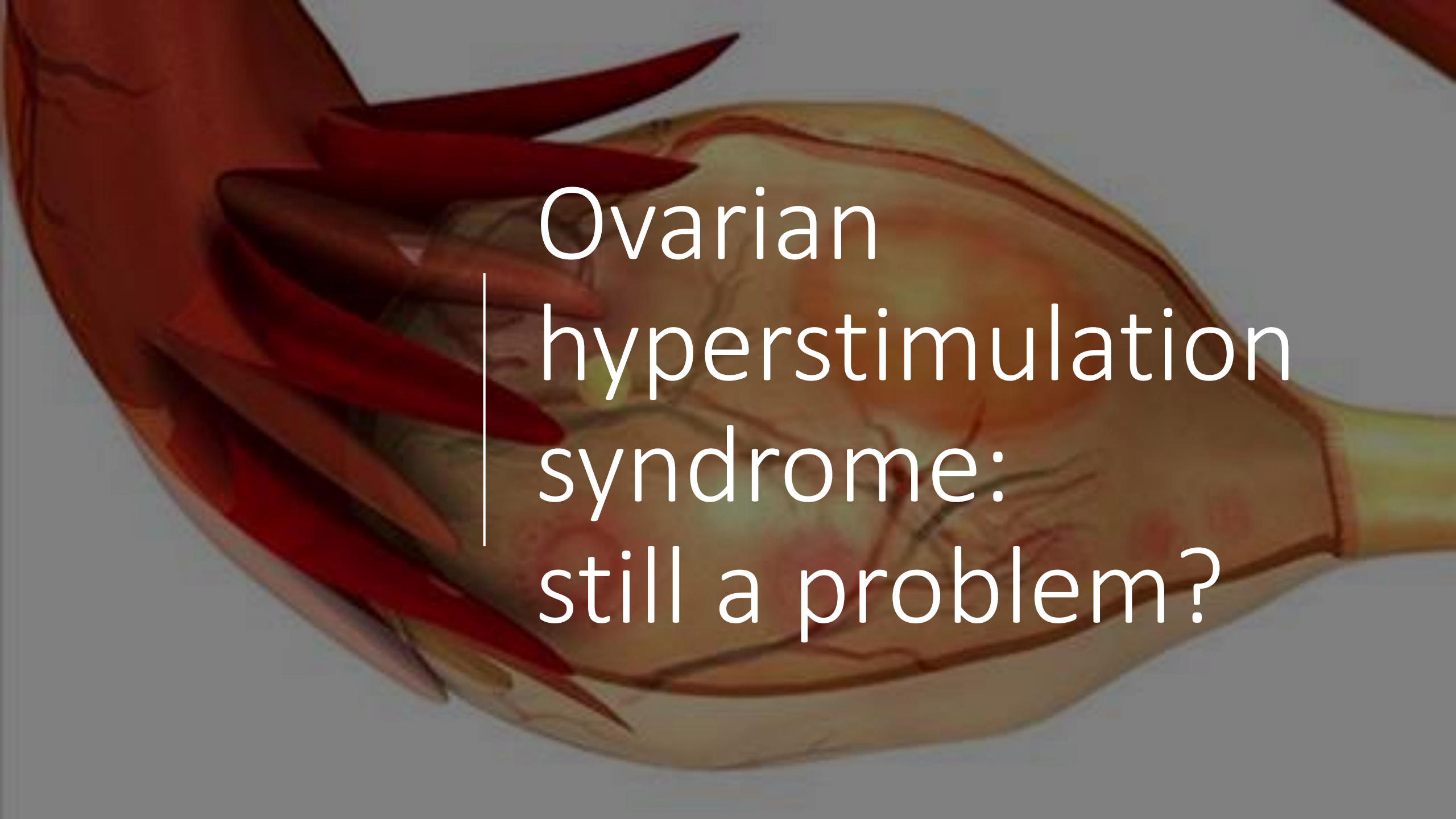
- Segmentation cannot prevent early onset OHSS if hCG is used to trigger maturation: **preventive measures are still fundamental**
- Cases of OHSS have still been reported even after GnRHan protocols and GnRHa trigger.

Freeze-all approaches cannot be considered the ultimate solution

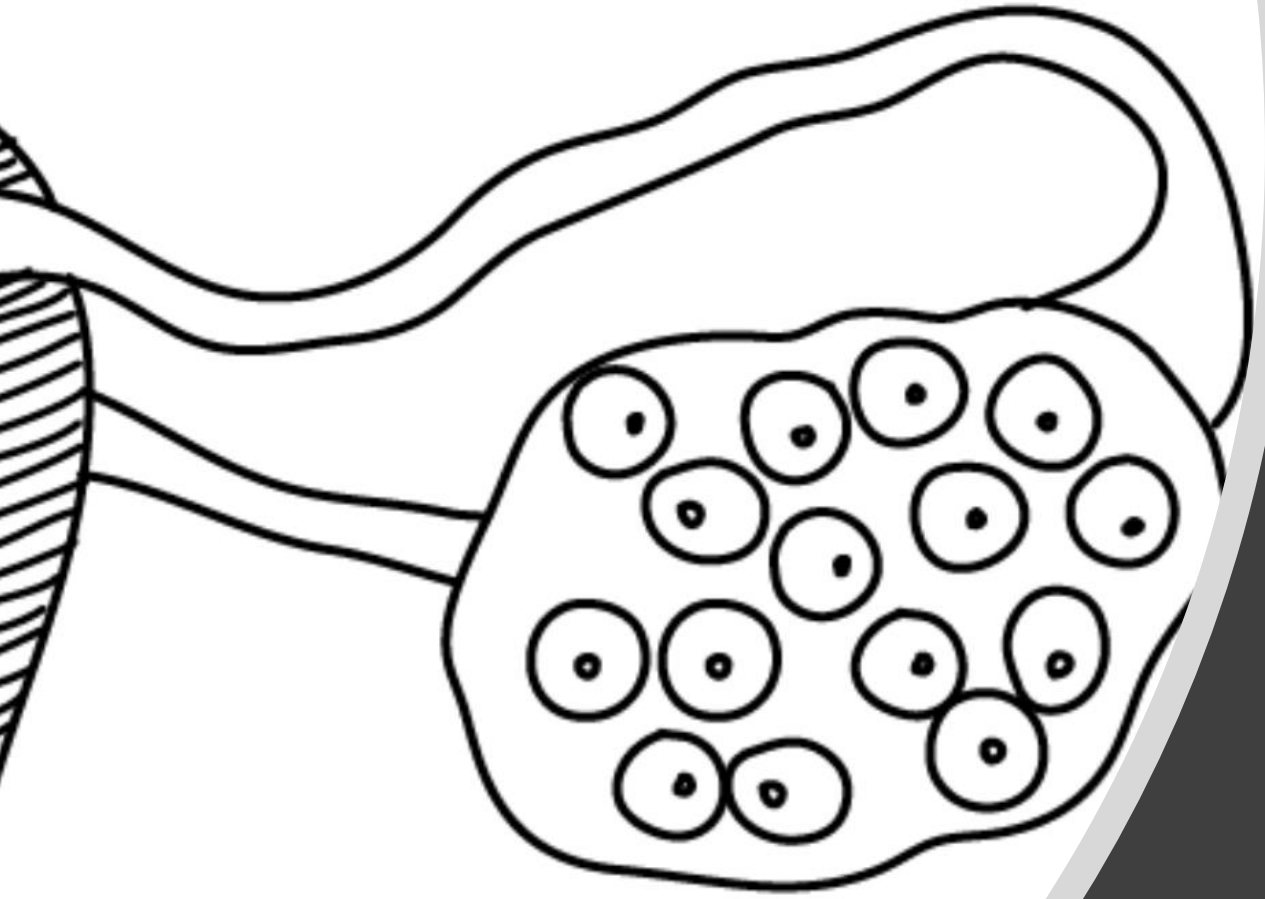
ERASE THE RISK OF OHSS?

- ✓ Adoption of **pre-treatment biomarkers** to individualize doses of exogenous gonadotropins
- ✓ Use of **GnRHan protocols** in all suspected high responders or in first iVF cycle patients
- ✓ **Shift from using hCG** for final oocyte maturation
- ✓ **Segmentation** of the cycle

GOOD BALANCE BETWEEN SAFETY AND TREATMENT OUTCOMES



Ovarian hyperstimulation syndrome: still a problem?



Thank you for your attention!