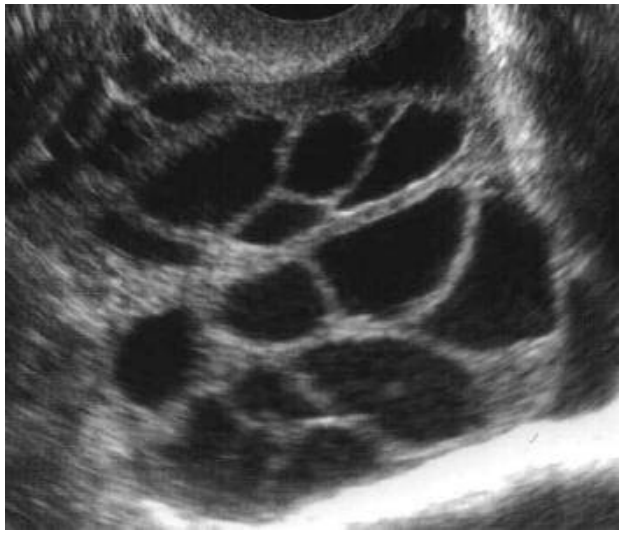
OHSS – Have we found a solution?

YES



Dr. Madhuri Patil

M.D., DGO, FCPS, DFP, FICOG. (Mum)

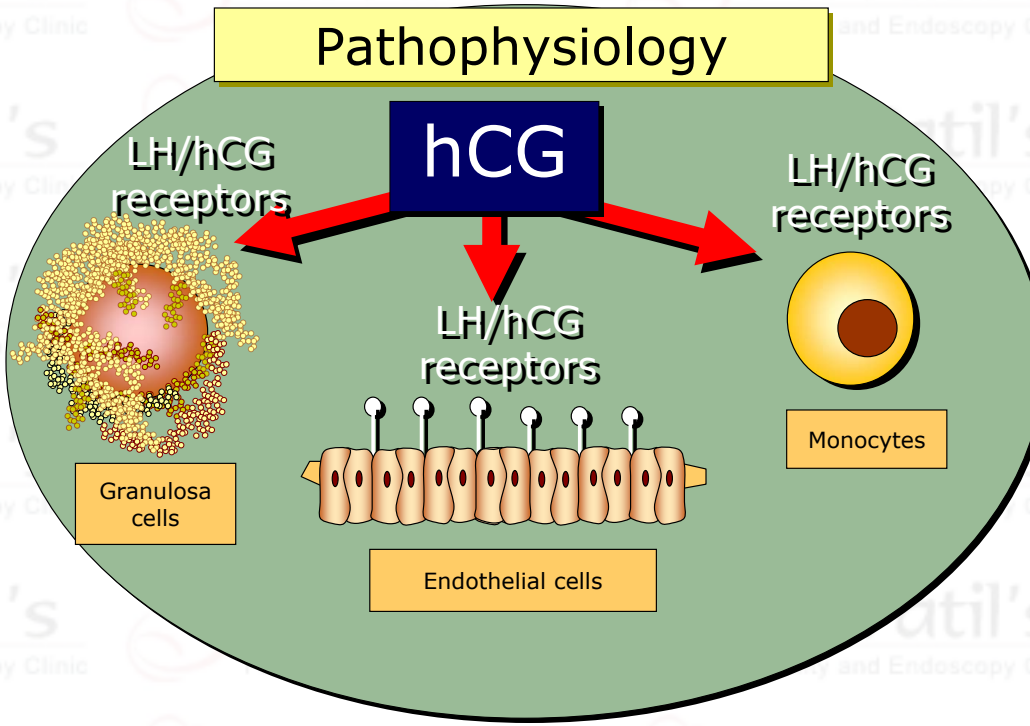
Dr. Patil's Fertility & Endoscopy Clinic

Bangalore

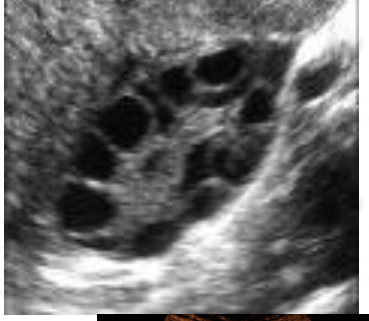
Ovarian hyperstimulation syndrome

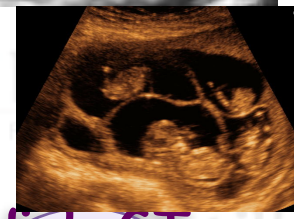
Serious and detrimental complication of ART due to

- ☑ **Ovarian stimulation**
- ☑ **HCG used for triggering**



Incidence and risk factors





All women undergoing COS should be considered potentially at risk of OHSS

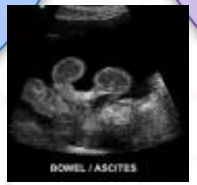
Mild to Moderate OHSS - 0.6 to 14% of 'conventional' IVF cycles

Severe OHSS 0.2-0.5%

Incidence in 'modified' and 'mild' stimulation protocols is unknown, but likely to be lower

Increased risk if

- PCOS
- Excessive ovarian response
- Younger women < 30 years
- Low BMI
- High GT dose for OI
- Increased hCG exposure – LPS with hCG and MP
- Previous OHSS



Mozes, Lancet 1965

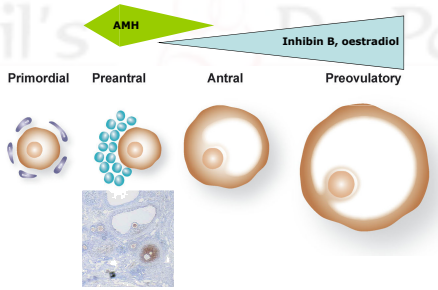
García Velasco & Pellicer, 2002

Risk factors

Prior AMH level

at cut off 3.36 ng/ml

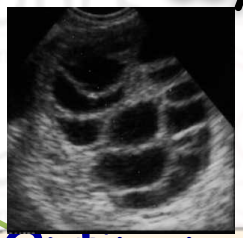
Sensitivity of 90.5%
Specificity of 81.3%

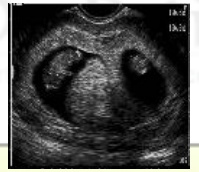


Blood group A
associated with early-onset OHSS, putatively via elevated VWF and factor VIII

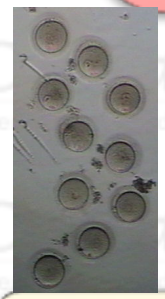
Rapidly increasing E2 levels of > 75% from previous day

E2 > 3500 pg/ml on day of hCG





Occurrence of pregnancy



> 20 oocytes retrieved

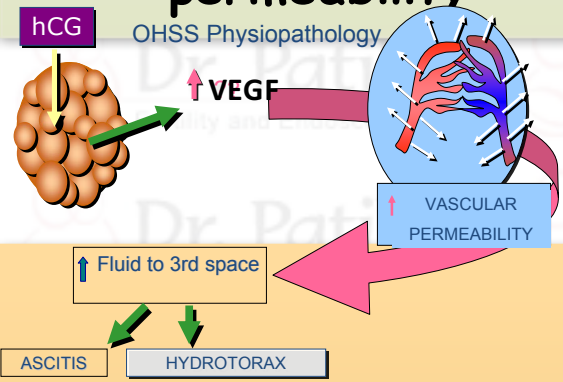
Optimum Cut off value for AFC = >14

Sensitivity 82 %

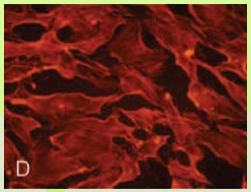
Specificity 89 %

PATHOPHYSIOLOGY

Increased vascular permeability



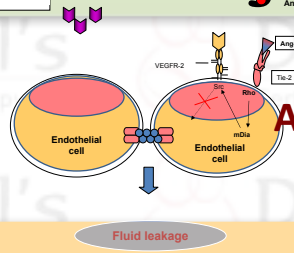
Arteriolar vasodilation



• sVE-Cadherin

VASCULAR PERMEABILITY

Ovarian enlargement



Angiopoietin 2

MAIN CLINICAL FEATURES

Ascites

Intravascular dehydration

SEQUELAE

Thromboembolism	Renal dysfunction	ARDS	Liver dysfunction
1 - 10 %	30 %	10- 12 %	25 %

OHSS – classification of severity

Mild

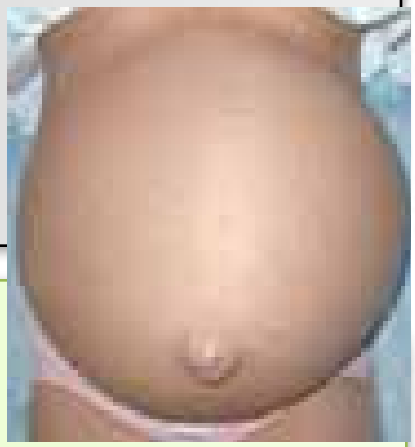
- Abdominal bloating
- Mild pain
- Ovaries <8 cm

Moderate

- Moderate abdominal pain
- Nausea,
- Diarrhoea

Ultrasound evidence of ascites

Ovaries usually 8 – 12 cm

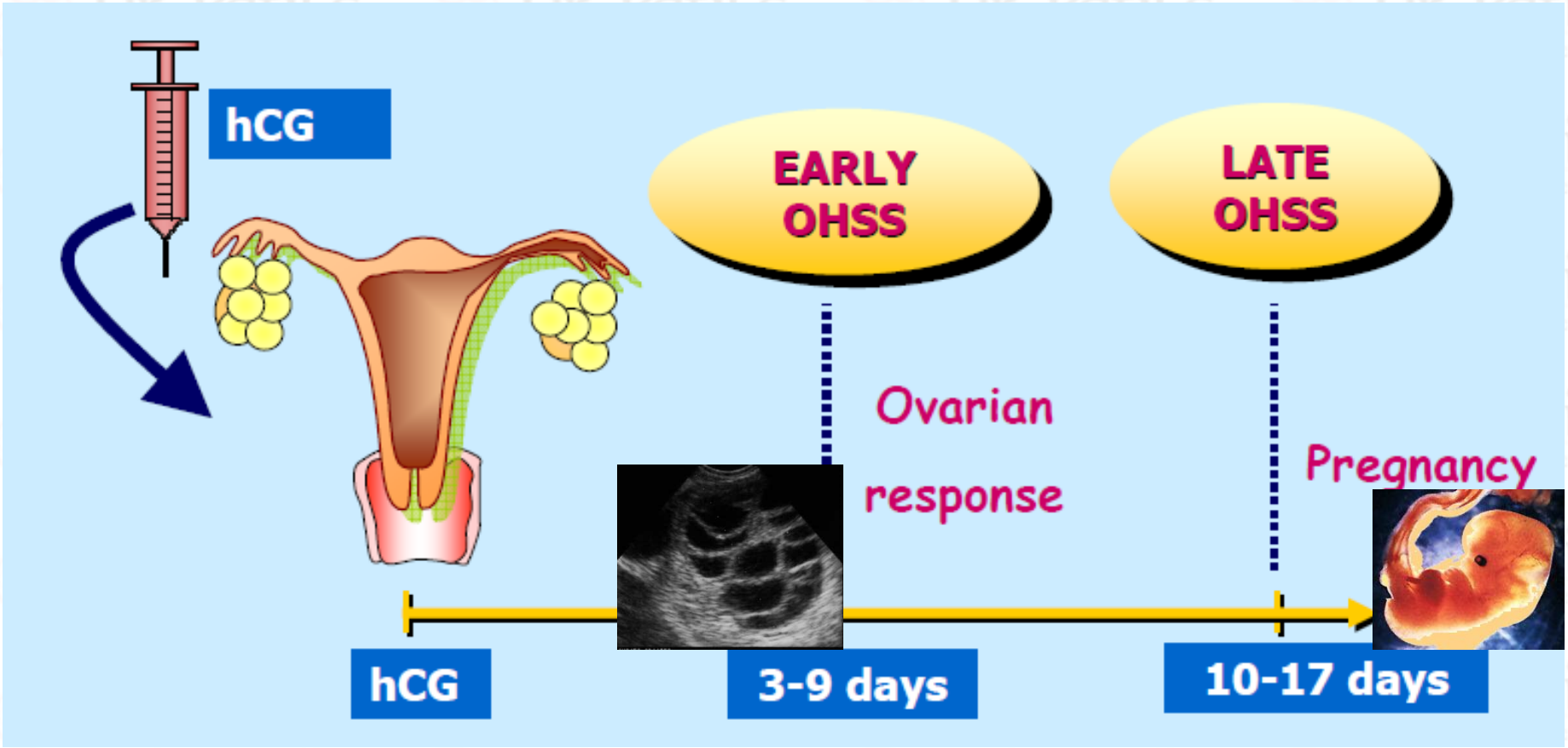


Severe

- Clinical ascites
- Hydrothorax.
- Haemoconcentration (Hct >45%, WBC >15,000/ml)
- Oliguria, Liver dysfunction
- Ovaries usually >12 cm

(Mathur et al 2005, modified from Navot et al 1989

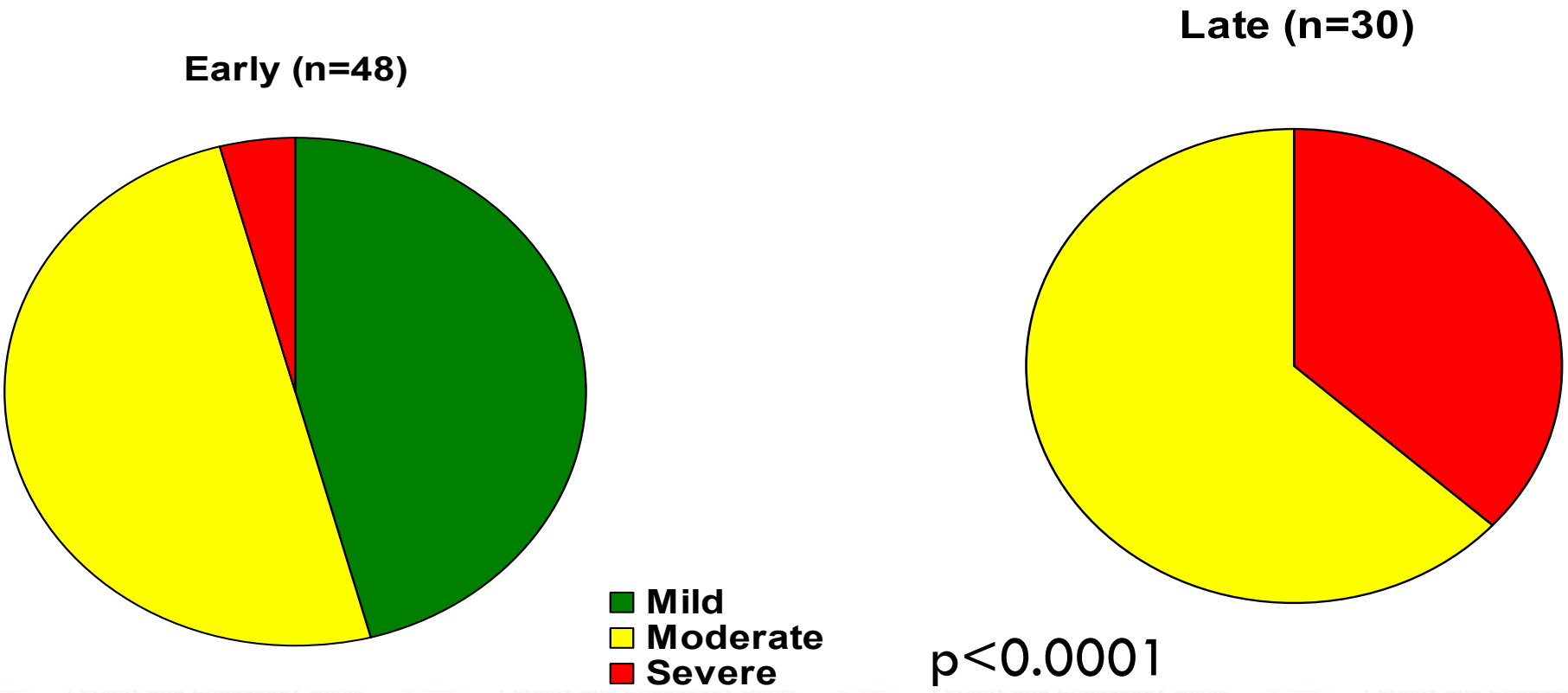
Classification



Dahl Lyons, 1994; Mathur, 2000

In its severest form, may have
serious impact on the patient s health
cause severe morbidity and even mortality

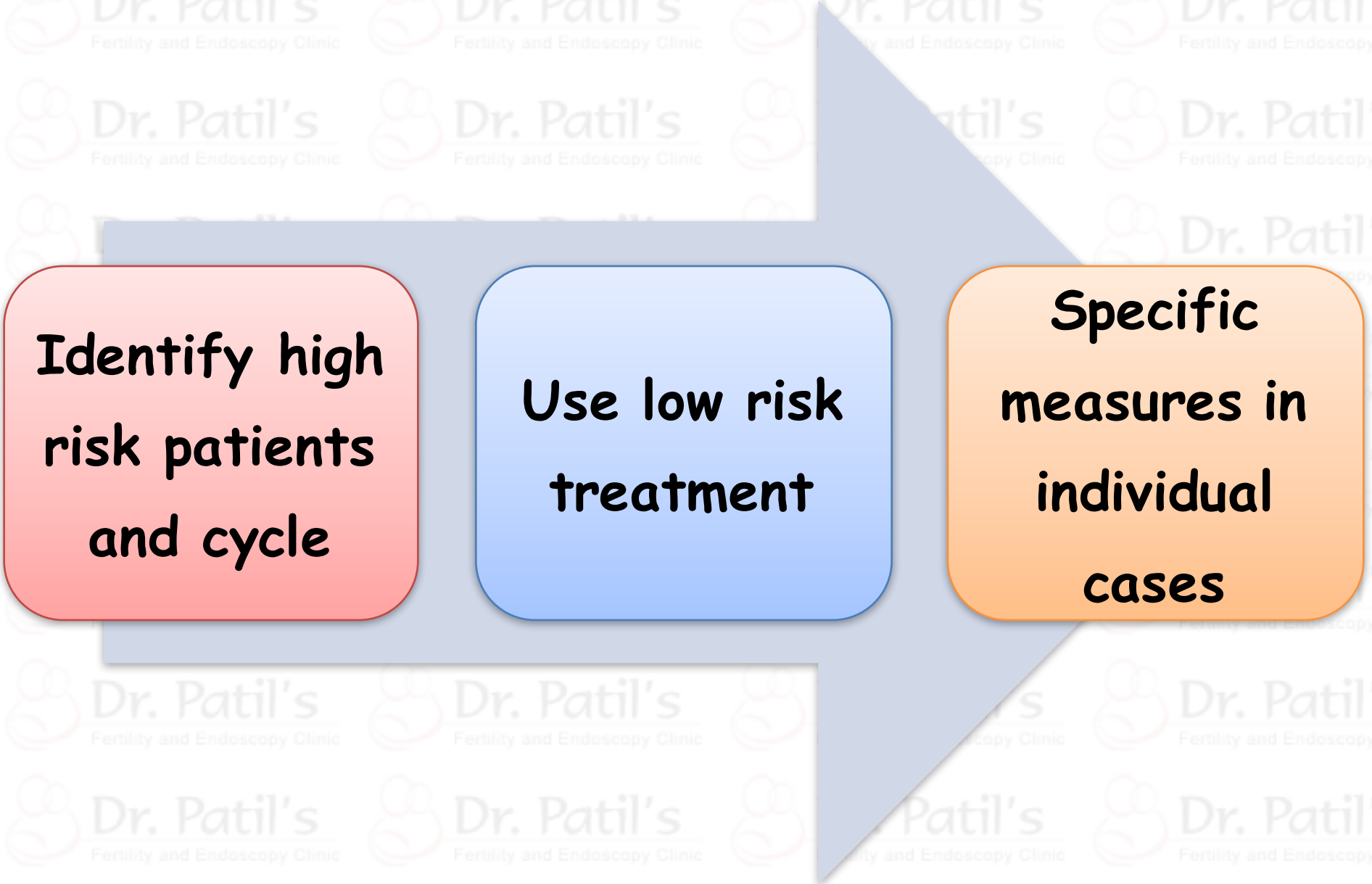
Late OHSS is more likely to be severe than early OHSS



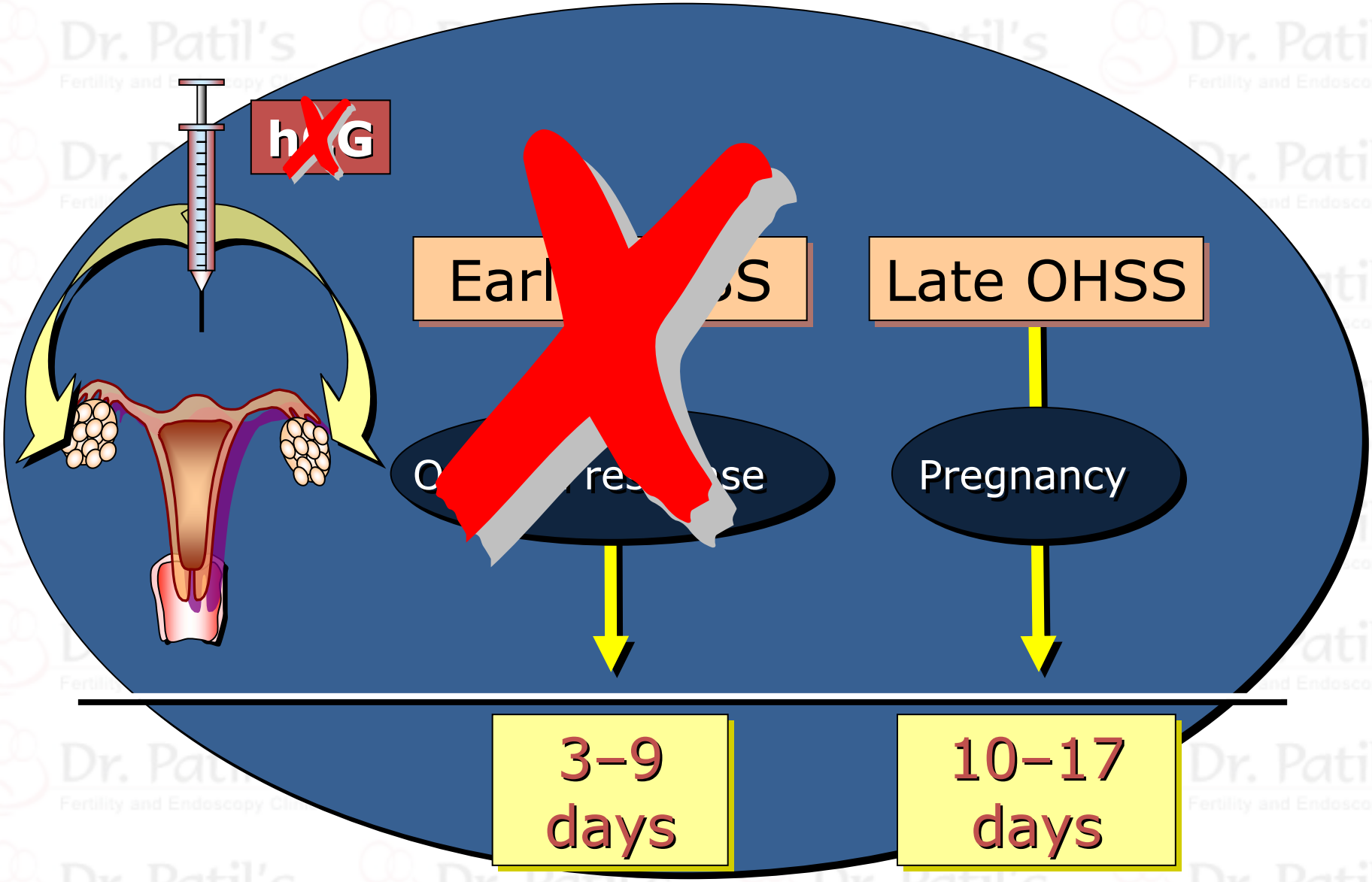
Late OHSS is more difficult to predict from ovarian response

Mathur et al., 2000 Fertil Steril 73, 901-12

Prevention of OHSS

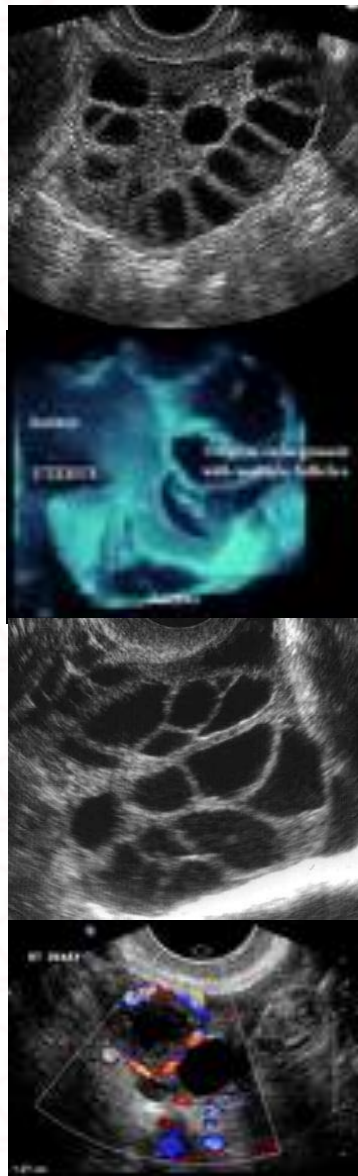


OHSS Prevention

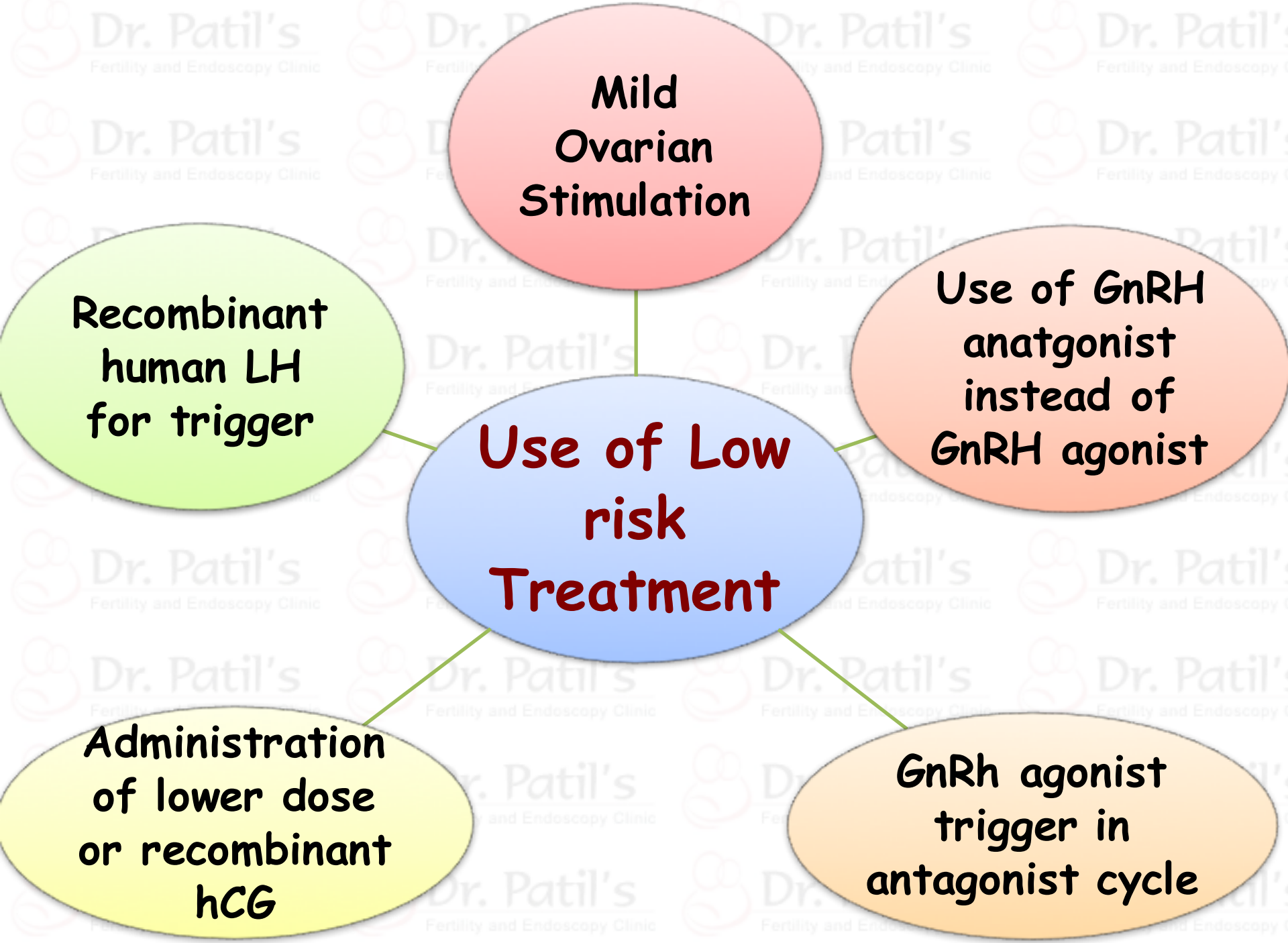


Lyons et al. 1994; Mathur et al. 2000

Caution is indicated when any of the following indicators for increasing risk of OHSS are present during COS:

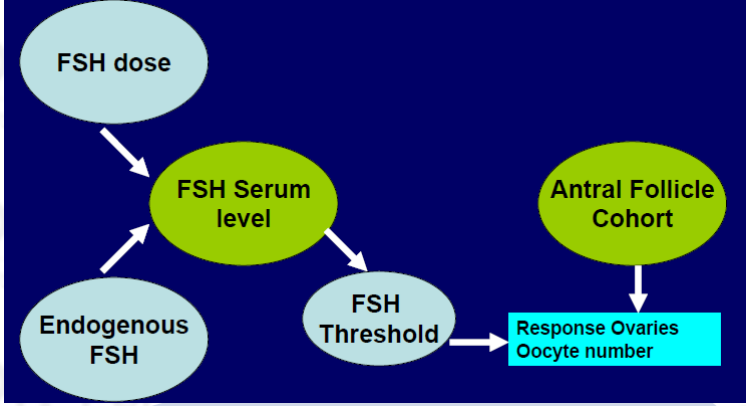


- ✓ The emergence of large number of small and intermediate sized follicles (10–14 mm) on USG
- ✓ Presence of > 8 – 10 dominant follicles
- ✓ Enlarged ovaries
- ✓ Presence of free fluid in POD
- ✓ Rapidly rising serum E2 levels
- ✓ E2 > 3500pg/ml on day of hCG


Mild Ovarian Stimulation
Recombinant human LH for trigger
Use of GnRH anatgonist instead of GnRH agonist
Use of Low risk Treatment
Administration of lower dose or recombinant hCG
GnRh agonist trigger in antagonist cycle

Gonadotropin Administration

Key to prevention of OHSS



Experience with OI therapy and recognition of risk factors for OHSS

Highly individualized OI regimens carefully monitored with USG and E2

Use of minimum dose and duration of GT therapy necessary to achieve the therapeutic goal

Lower oocyte numbers and E2 concentrations may be surrogate markers of a lower risk of OHSS

GnRH antagonist vs agonist

2.1 % vs 3.3 %

Papanikolau et al (2006) Fertil Steril
Mathur et al (2000) Fertil Steril

Potential for using GnRH agonist triggering of ovulation which has lower OHSS risk than hCG trigger ✔

Cochrane Meta-analysis shows a reduced incidence and interventions for OHSS with antagonist vs agonist

(Al-Inany et al 2006)

Administration of lower dose of hCG

- hCG 2500 - 5000 IU as against standard 10000 IU or Rec-hCG 250mcg instead of 500 mcg
- 250 mg rhCG and 5000 IU hCG produced comparable results
- Significantly lower successful oocyte recovery in patients who received 2000 IU hCG
  Abdalla et al., 1987
- PR, IR and OHSS rate were similar with urinary and recombinant hCG
  Driscoll et al., 2000; The European Recombinant Human Chorionic Gonadotrophin Study Group, 2000; Chang et al.,2001

Administration of Recombinant LH

5000 – 30000 IU up to 10000 IU safe

Effective in inducing final follicular maturation and early luteinization and was comparable with 5000 IU urinary hCG

Resulted in a highly significant reduction in OHSS as compared to hCG

Shoham Z, Schacter M, Loumaye E, Weissman A, Macnamee M, Insler V

Administration of GnRh agonist instead of hCG for trigger

Substitution of hCG by single GnRH agonist bolus is the safest protocol and avoids cycle cancelation

GnRha SC in cycles not involving previous DR with long agonist protocols or when GnRH antagonist used

Excellent results obtained with egg or embryo vitrification

Avoid both early- and late-onset OHSS, while eliminating the need for adequate and specific luteal support

(Kuwayama et al., 2005; Cobo et al., 2008)

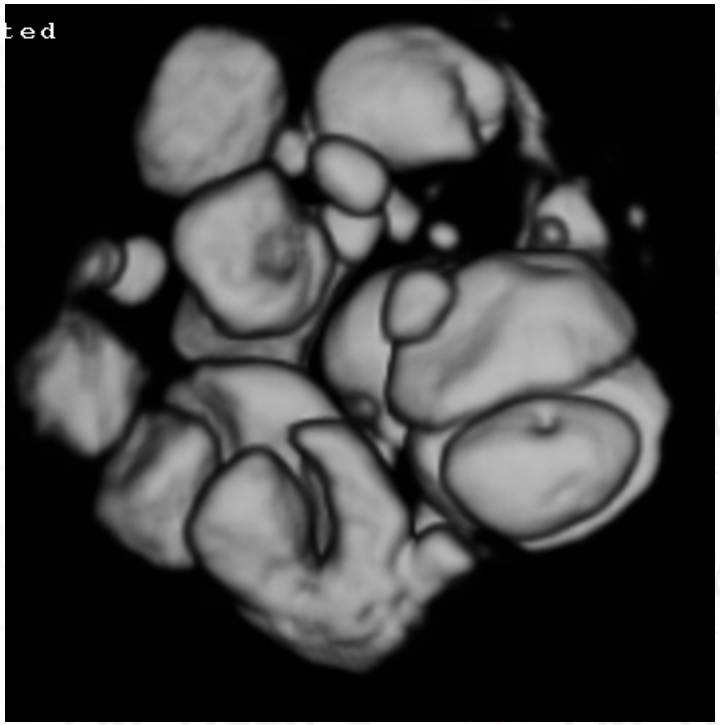
Single GnRH agonist injection resulted in combined LH & FSH surges lasting 24 h

Gonen et al., 1990

GnRH agonist for triggering of ovulation

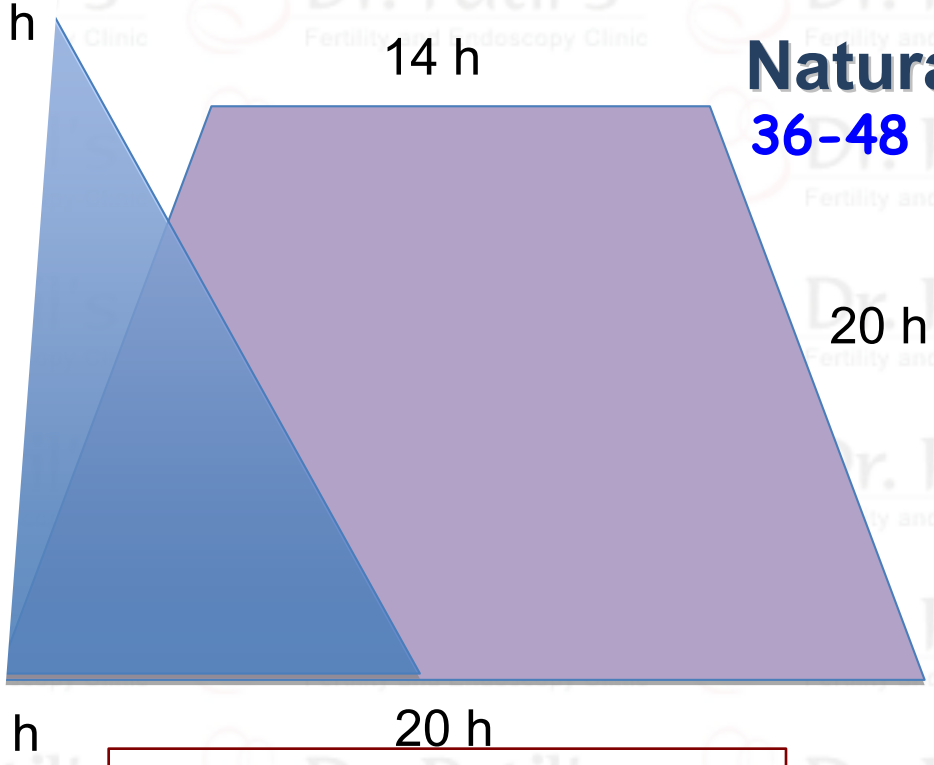
Most commonly used GnRHa triggering doses:

- Buserelin 0.5mg s.c
- Triptorelin 0.2mg s.c
- Leuprolide 1mg s.c



LH surge: GnRHa vs natural

Shorter plateau



GnRHa
20-24 h

Natural
36-48 h

Shorter ascending phase

Longer decending phase

Additional FSH surge

- induce LHR in GC
- promote oocyte nuclear maturation
- cumulus expansion
- suppression of intercellular coupling of cumulus cells

Hoffer, 1983; Gonen, 1990; Itskovitz, 1991

Administration of GnRh agonist instead of hCG for trigger

Massive and irreversible luteolysis after GnRHa trigger

Completely prevents early onset OHSS

Endogenous LH surge with short half-life results in defective CL development and significantly reduced total amounts of LH and FSH

Segal and Casper, 1992

Direct effect on endometrial receptivity

Administration of GnRh agonist instead of hCG for trigger

More physiological

Endogenous FSH surge

Steroid level in luteal phase closer to physiological condition

LP impacted severely by COS - So remove ovarian stimulation and then----?

hCG increase LH activity but does not reconstitute the midcycle physiologic FSH surge

Causes rise in intrafollicular P4

Development of multiple corpora lutea

T1/2 endogenous LH shorter for GnRHa - 20 mins as against 33 hours with hCG

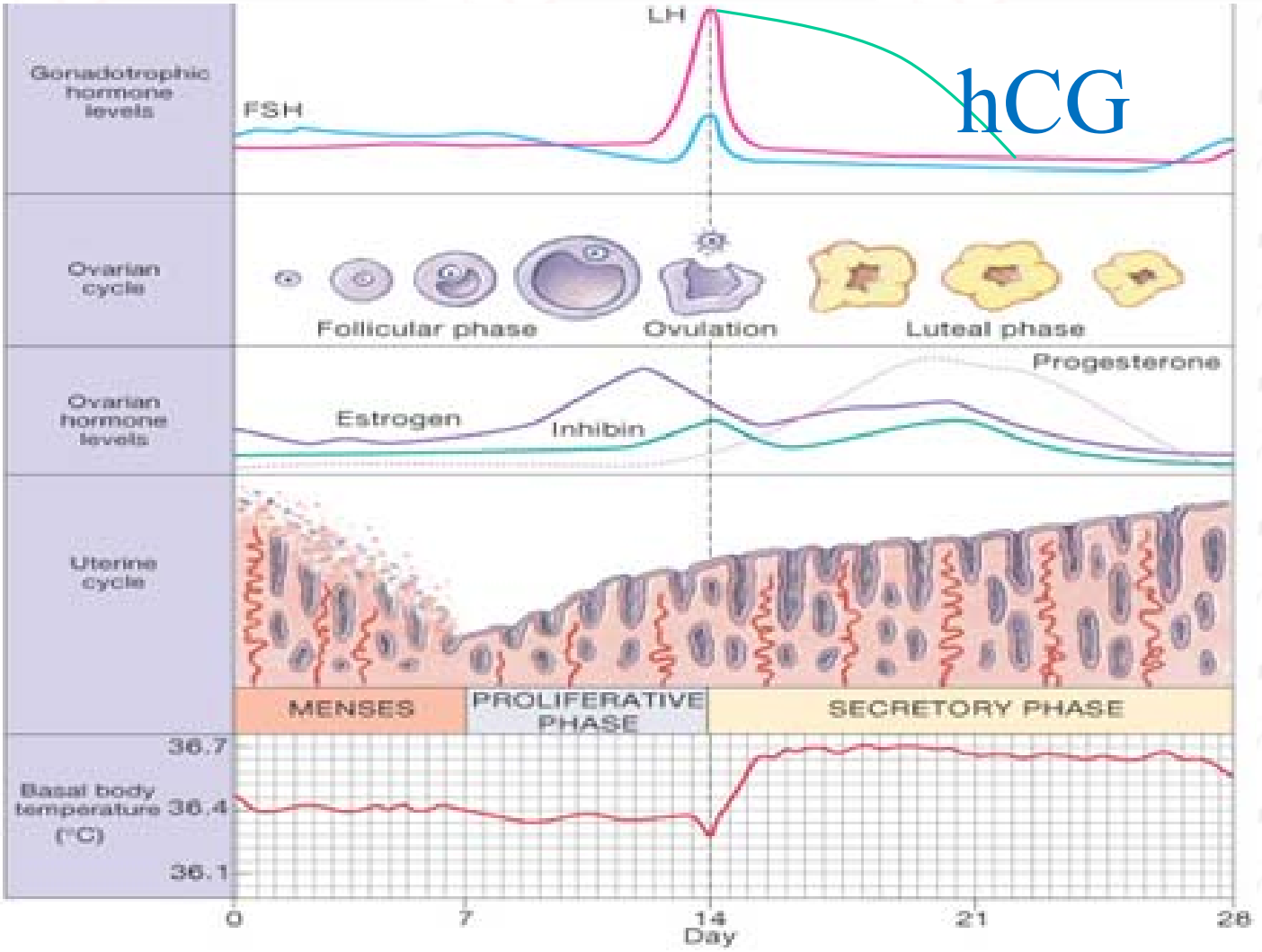
Simpler cycle monitoring with less or no E2 assay

No coasting or cycle cancellation

More MII oocytes harvested in IVF with GnRHa

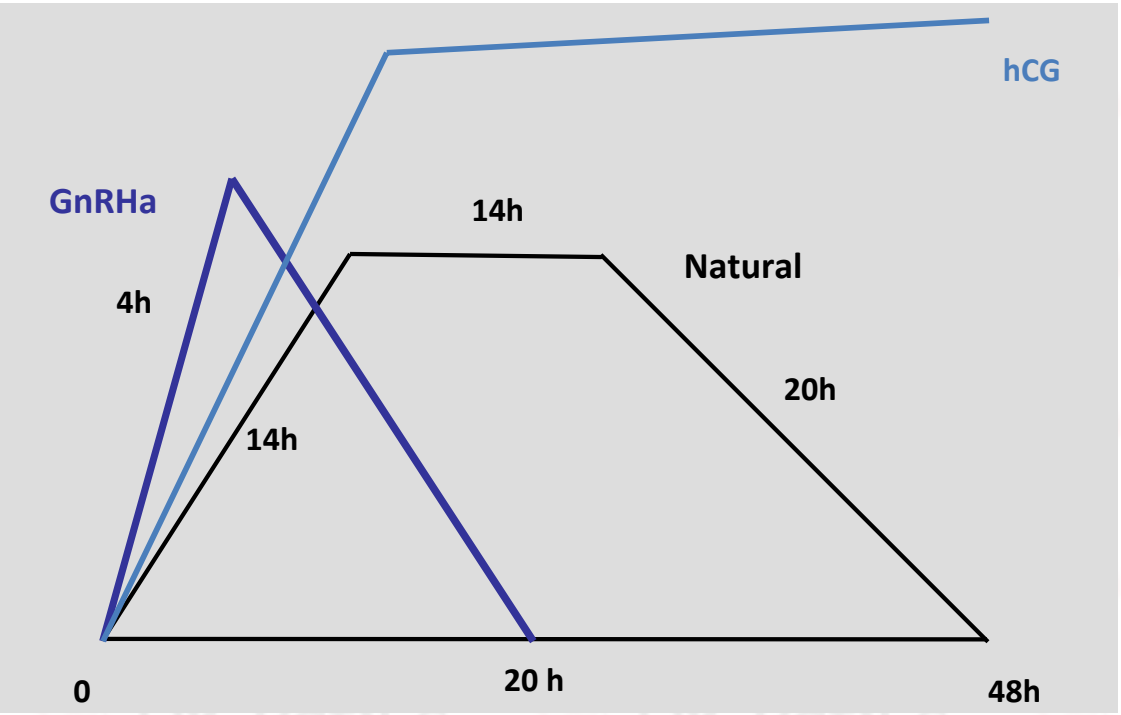
Similar oocyte and embryo quality

Dual role of hCG trigger



- Final oocyte maturation
- Early luteal phase stimulation resulting in almost normal Luteal function
- Same dose for both functions?

hCG versus GnRH agonist



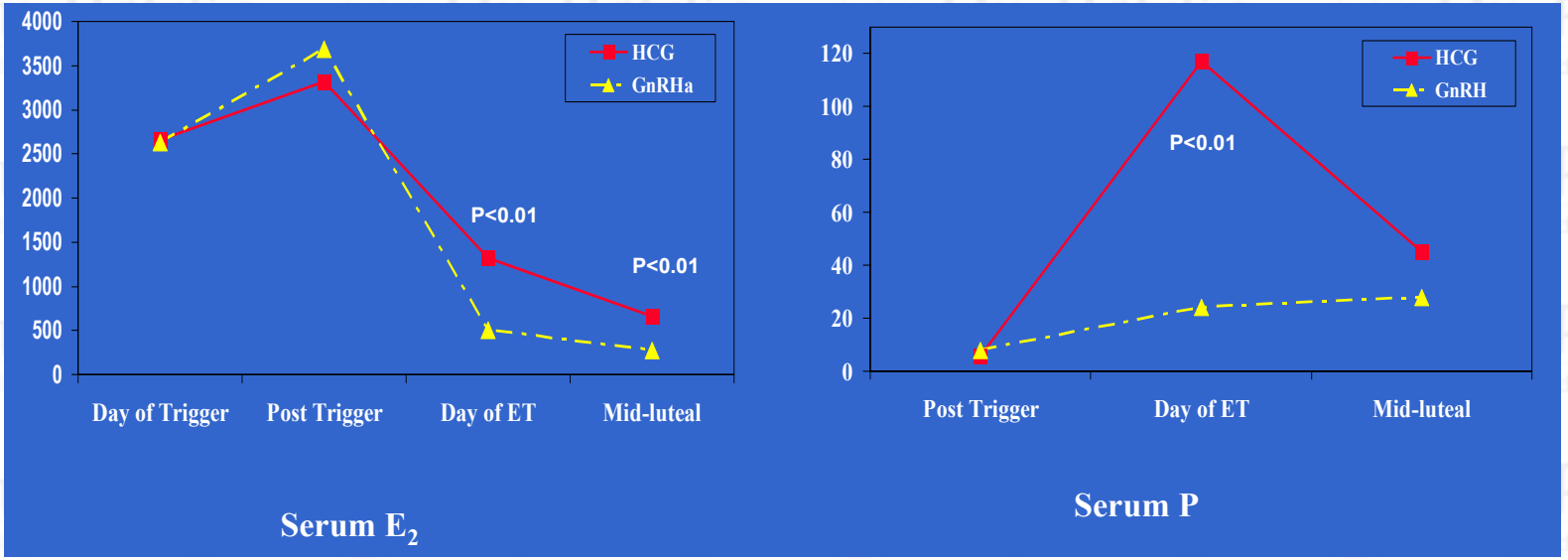
Duration of LH surge

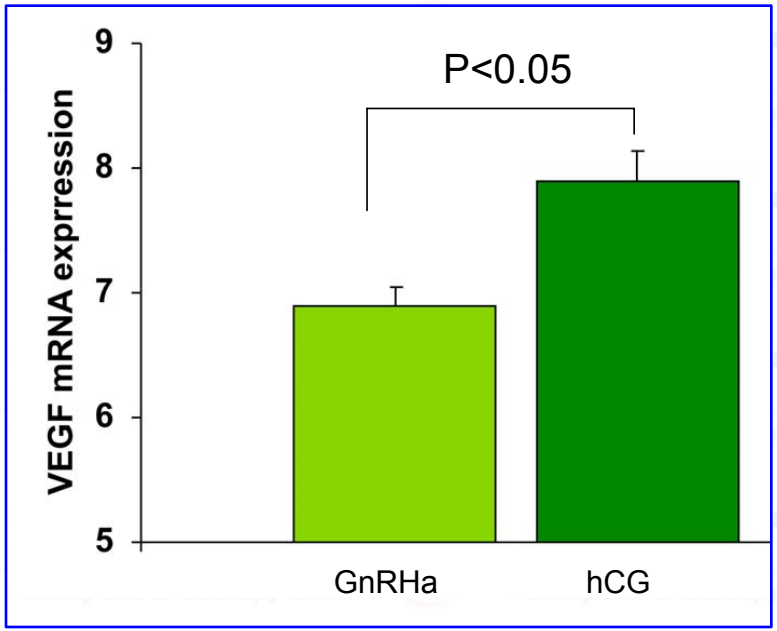
LH mean mid-luteal phase

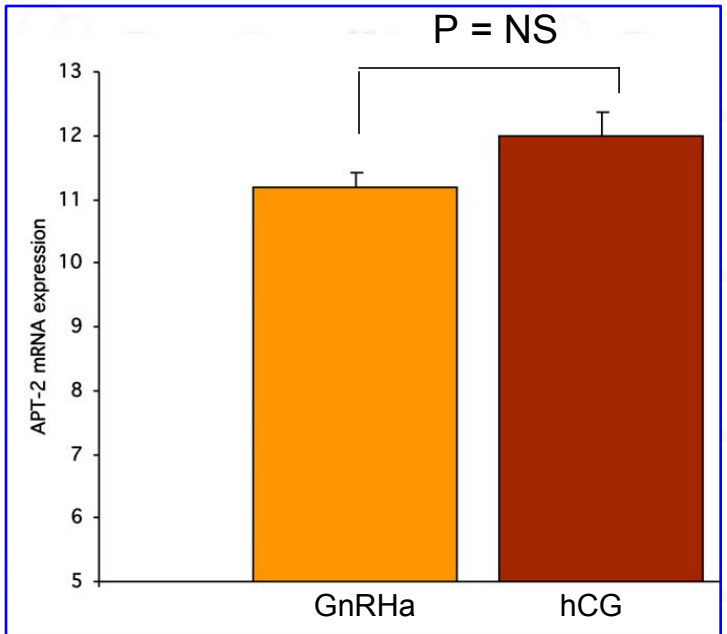
- 6.0 IU/l in natural cycle
- 1.5 IU/l in GnRH a group
- 0.2 IU/l in hCG group

(Tavaniotou and Devroey2003)
(Humaidan etal, 2005)

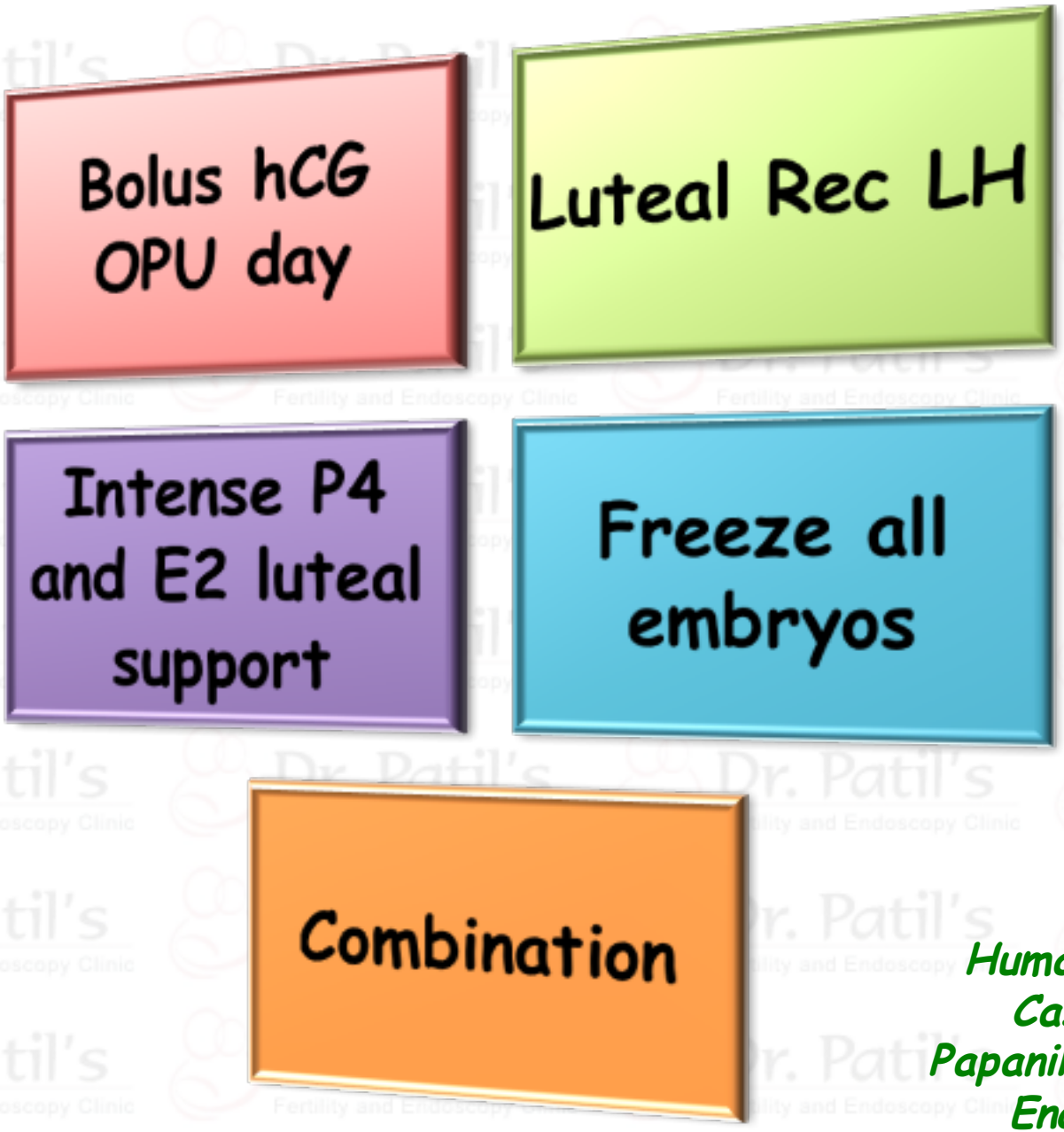
hCG versus GnRH agonist







Strategies after GnRH agonist Trigger



Humaidan et al 2010
Castillo et al 2010
Papanikolau et al 2010
Engman et al 2008

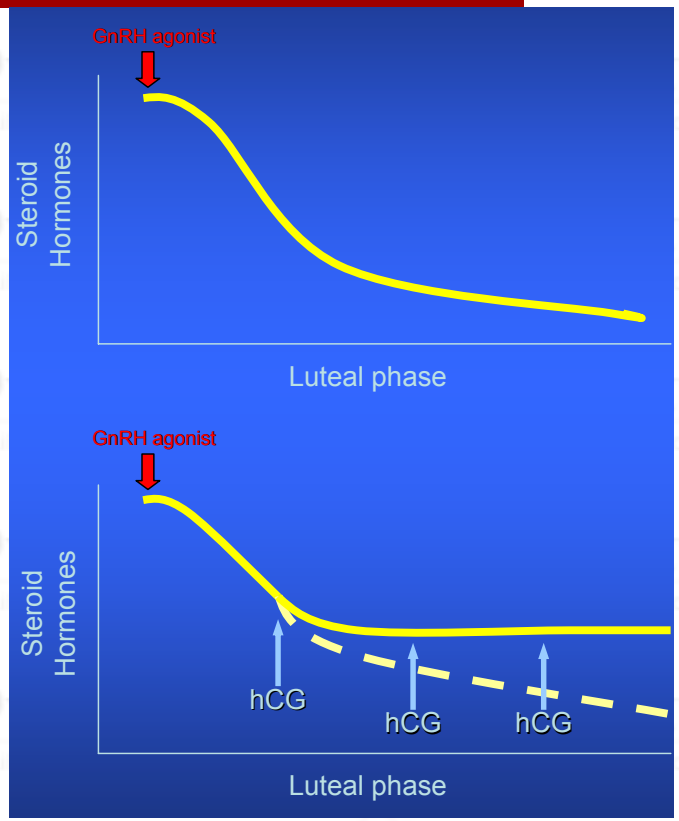
Personalized luteal phase support

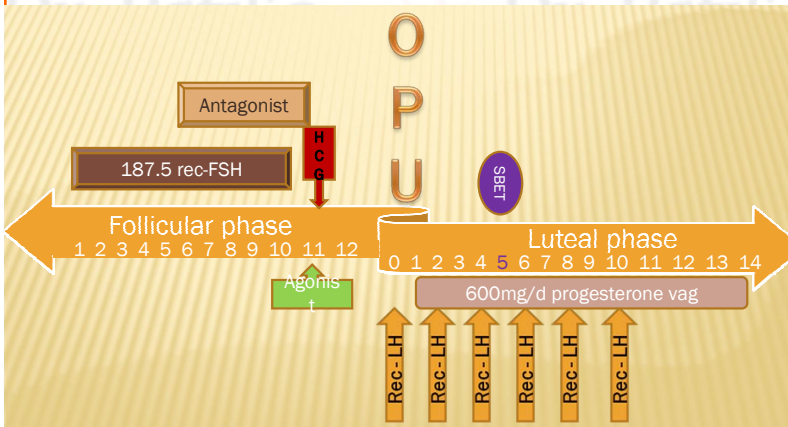
Normo-responder patient (< 14 follicles)

Repeat bolus of hCG (1500 IU, OPU + OPU+5) + E2/P4 (Micronized vaginal progesterone 90 mg/day + Oestradiol 4 mg/day) until 7 weeks

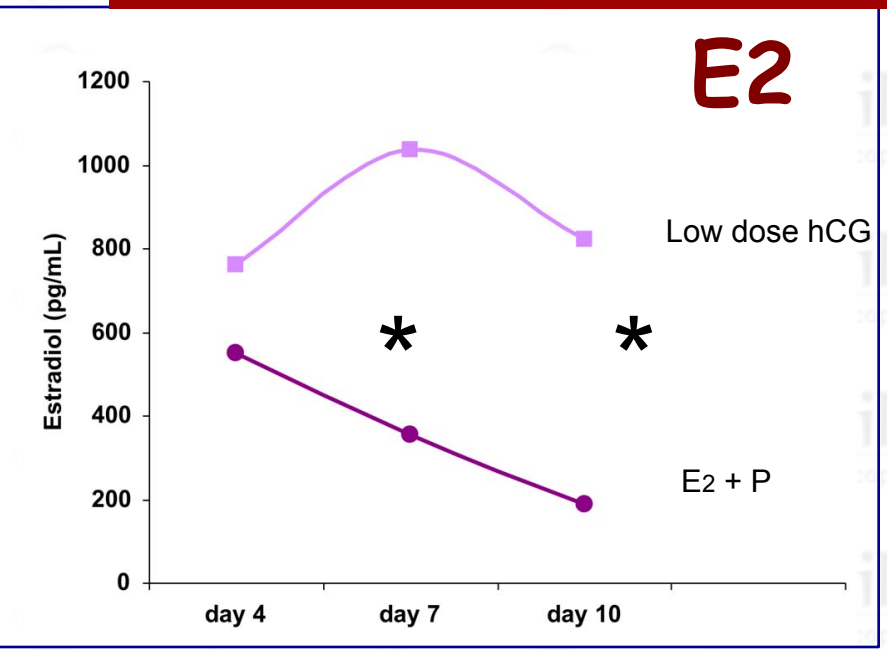
OHSS risk patient

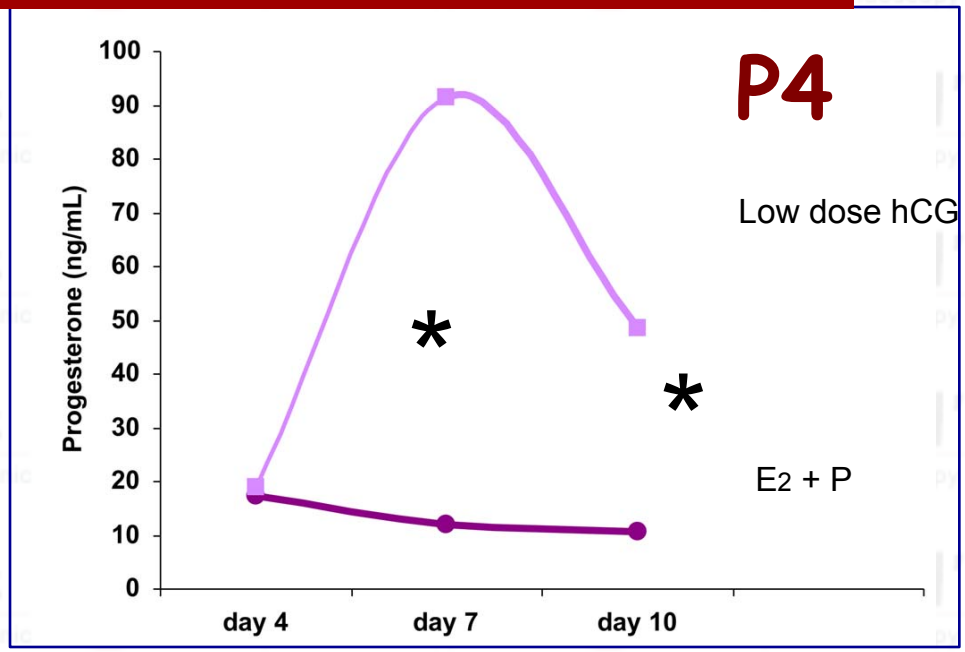
- One bolus of hCG (1500 IU, OPU) + E2/P4 (Micronized vaginal progesterone 90 mg/day + Oestradiol 4 mg/day) until week 7
- Rec LH for 10 days from day of OPU
  5000 – 30000IU
  10000 IU adequate but ideal dose needs to be evaluated
- Total freeze

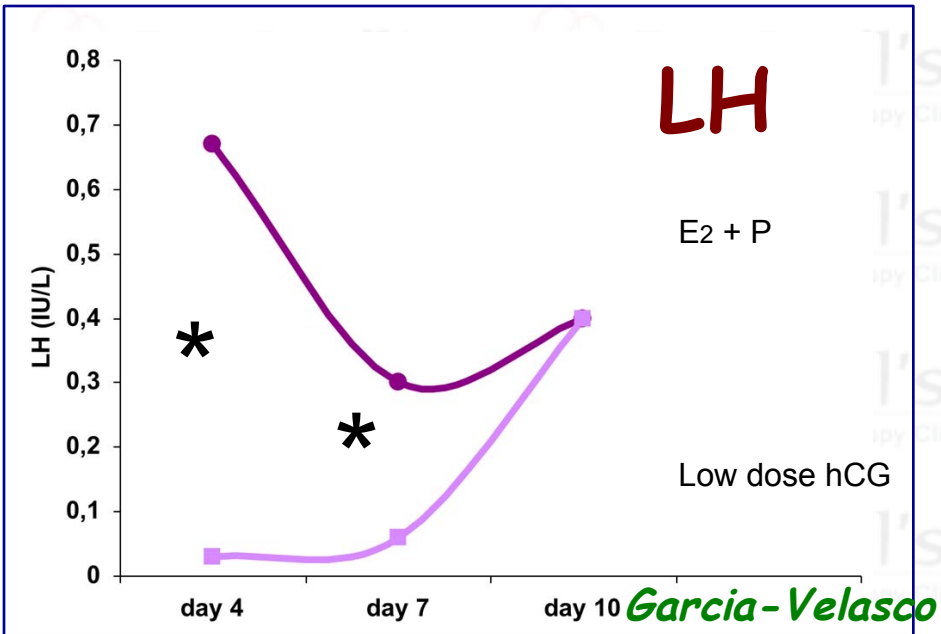


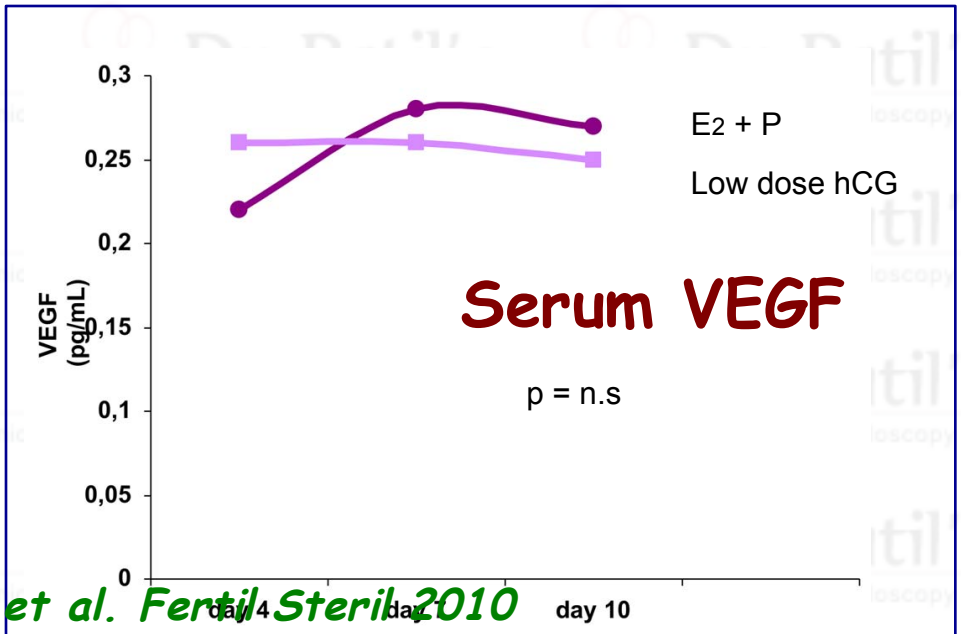


Hormonal Profile - hCG+P4+E2 vs P4+E2



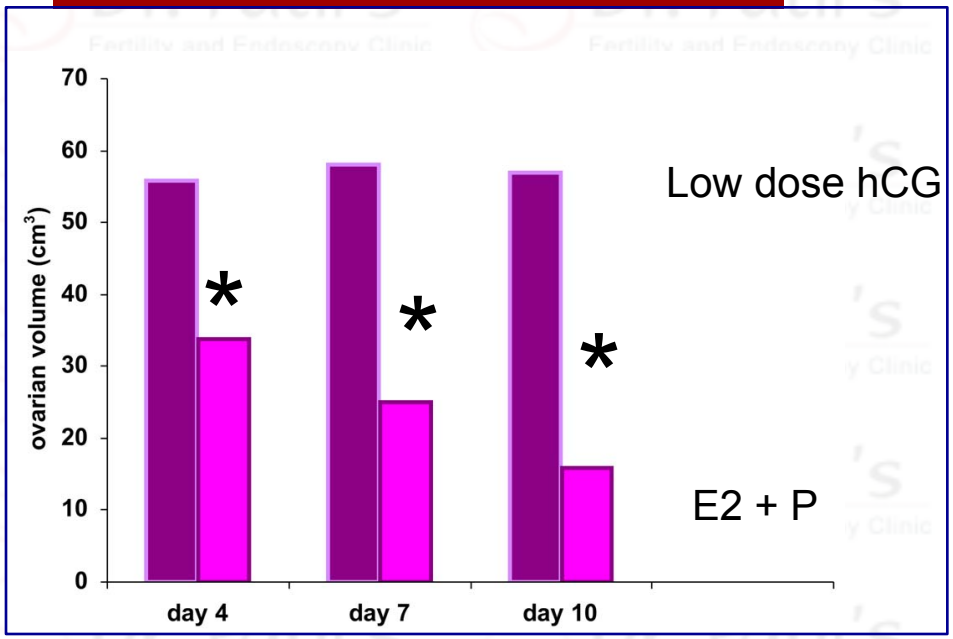




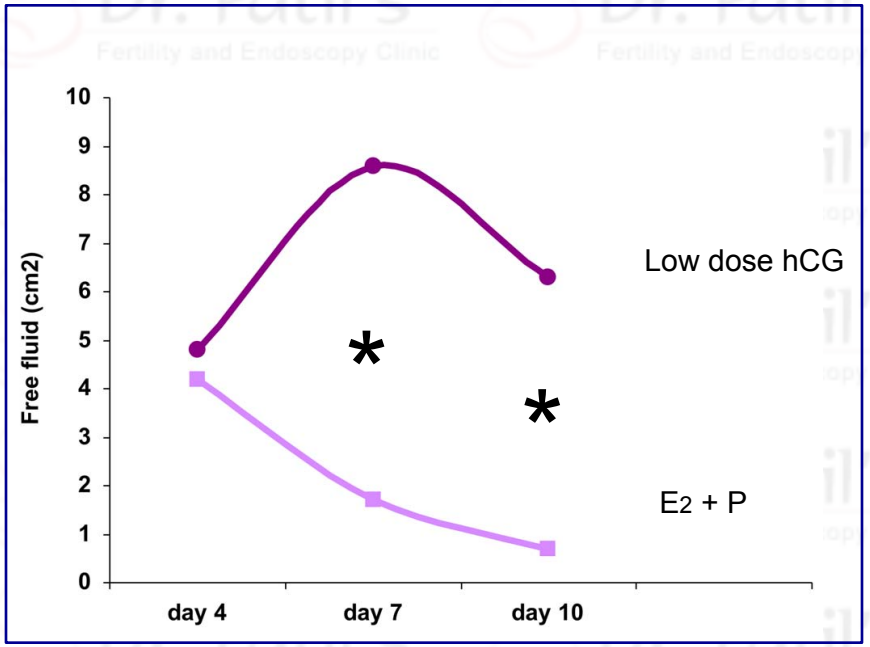


Garcia-Velasco et al. Fertil Steril 2010

Ovarian volume



Free fluid (cm2)

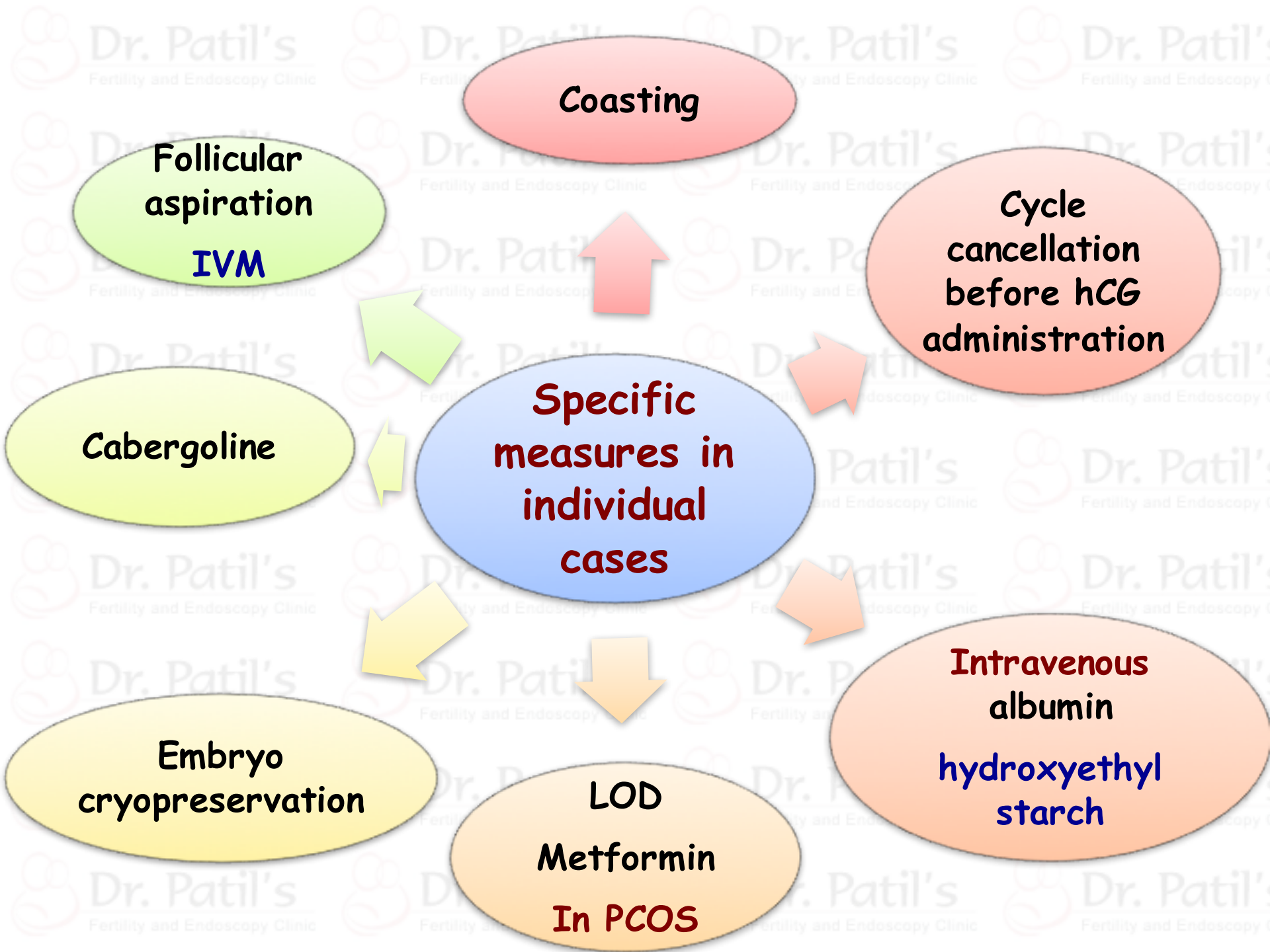


Garcia-Velasco et al. Fertil Steril 2010

16 publications GnRH Agonist trigger: 2005 patients, not a single case of OHSS

hCG trigger: 92 cases in 1810 patients, 5.1%

Reference	Trial type	Oocyte source	Ovulation trigger	n	OHSS % (n)
Babayof et al 2006	RCT, high risk	own	GnRHa hCG	15 13	0 (0/13) 31(4/13)
Engamnn et al 2008	RCT, high risk	own	GnRHa hCG	33 32	0 (0/33) 31 (10/32)
Acevedo et al 2006	RCT	donors	GnRHa hCG	30 30	0 (0/30) 17 (5/30)
Bodri et al 2009	Retrospective	donors	GnRHa hCG	1046 1031	0 (0/1046) 1.3 (13/1031)
Griesinger et al 2010	Observational, High risk	own	GnRHa	40	0 (0/40)
Humaidan et al 2009	RCT	own	GnRHa hCG	152 150	0 (0/152) 2 (3/150)
Engmann et al 2006	Retrospective, case-controlled, high risk	own	GnRHa hCG	23 23	0 (0/23) 4 (1/23)
Manzanares et al 2009	Retrospective case-control, high risk	own	GnRHa hCG - cancelled	42	0 (0/42)
Hernandez et al 2009	Retrospective	donors	GnRHa hCG	254 175	0 (0/254) 6 (10/175)
Orvieto et al 2006	Retrospective, high risk	own	GnRHa hCG	82 69	0 (0/82) 7 (5/69)
Shapiro et al 2007	Retrospective, high risk: agonist arm only	donors	GnRHa hCG	32 42	0 (0/32) 1 (1/42)
Sismanoglu et al 2009	RCT	donors	GnRHa hCG	44 44	0 (0/44) 7 (3/44)
Humaidan et al 2009	Observational, high risk	own	GnRH, luteal rescue with hCG 1500IU	12	8 (1/12)
Galindo et al 2009	RCT	donors	GnRHa hCG	106 106	0 (0/106) 8 (9/106)
Melo at al 2009	RCT	donors	GnRHa hCG	50 50	0 (0/50) 16(8/50)
Shahrokh et al 2010	RCT, high risk	own	GnRHa hCG	4 45	0 (0/45) 15 (33)


Coasting
Follicular aspiration
IVM
Cycle cancellation before hCG administration
Cabergoline
Specific measures in individual cases
Intravenous albumin
hydroxyethyl starch
Embryo cryopreservation
LOD
Metformin
In PCOS

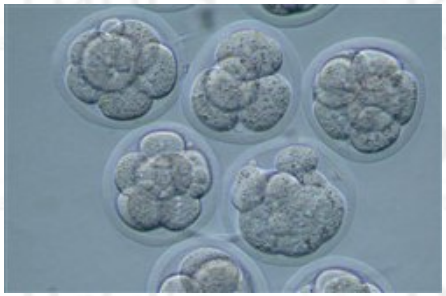
Cryopreservation of all embryos

Eliminates risk of late OHSS, but early OHSS can still occur if hCG given for trigger

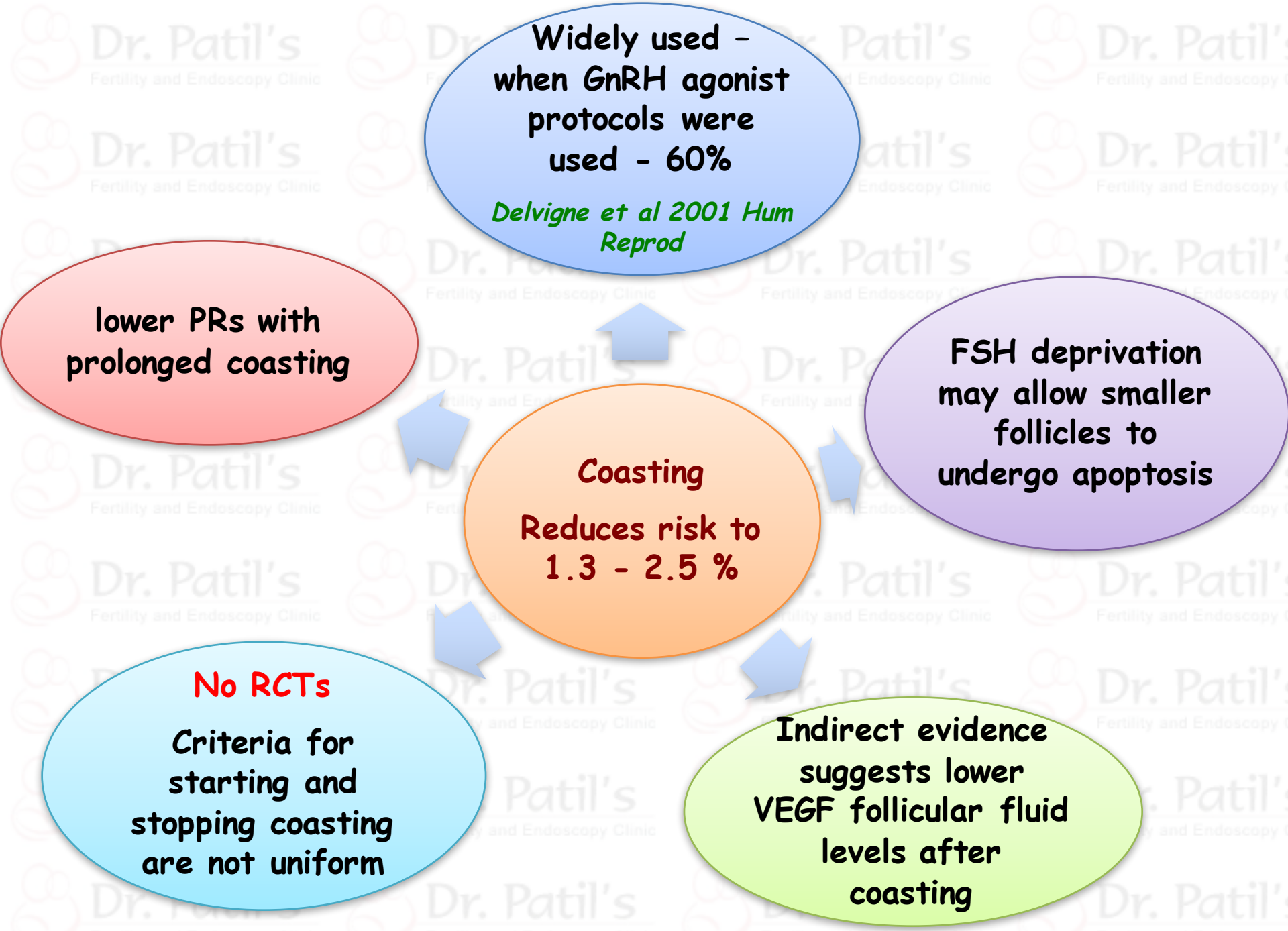
Patients may prefer this to cycle cancellation

Consider if patient symptomatic at the time of ET – blastocyst culture provides more time to evaluate

Continuation of GnRH agonist or antagonist reduces risk of OHSS by preventing endogenous LH surge



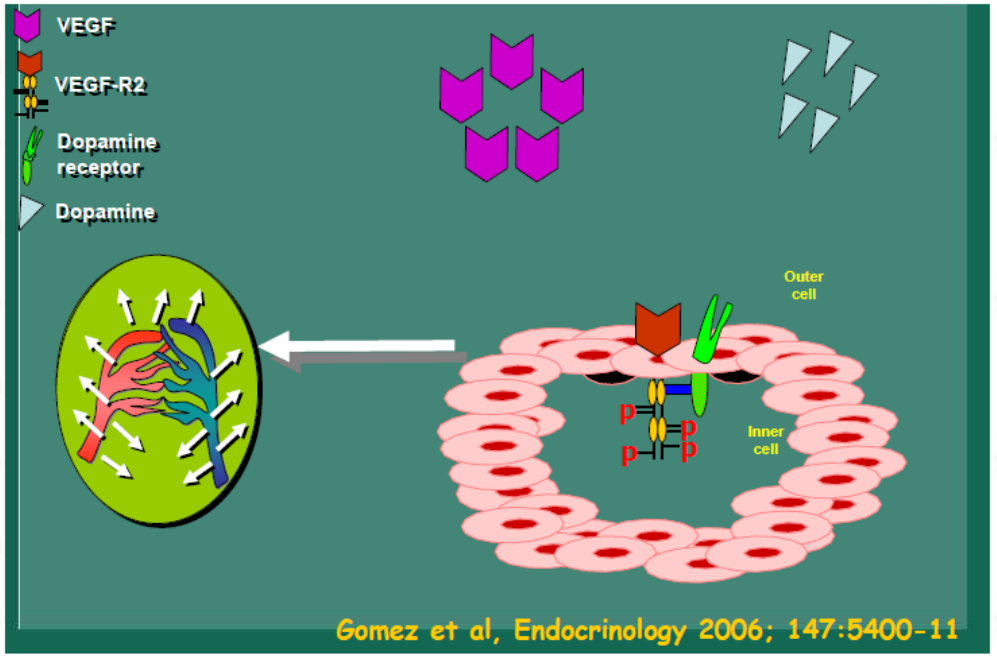
Endo et al 2002; Lainas et al 2007 RBM Online


Widely used – when GnRH agonist protocols were used - 60%
Delvigne et al 2001 Hum Reprod
lower PRs with prolonged coasting
FSH deprivation may allow smaller follicles to undergo apoptosis
Coasting
Reduces risk to 1.3 - 2.5 %
No RCTs
Criteria for starting and stopping coasting are not uniform
Indirect evidence suggests lower VEGF follicular fluid levels after coasting

Use of Dopamine Agonist

Cabergoline reduces the effects of VEGF-mediated vascular permeability without compromising IR and PR *Juan Garcia-Velasco*

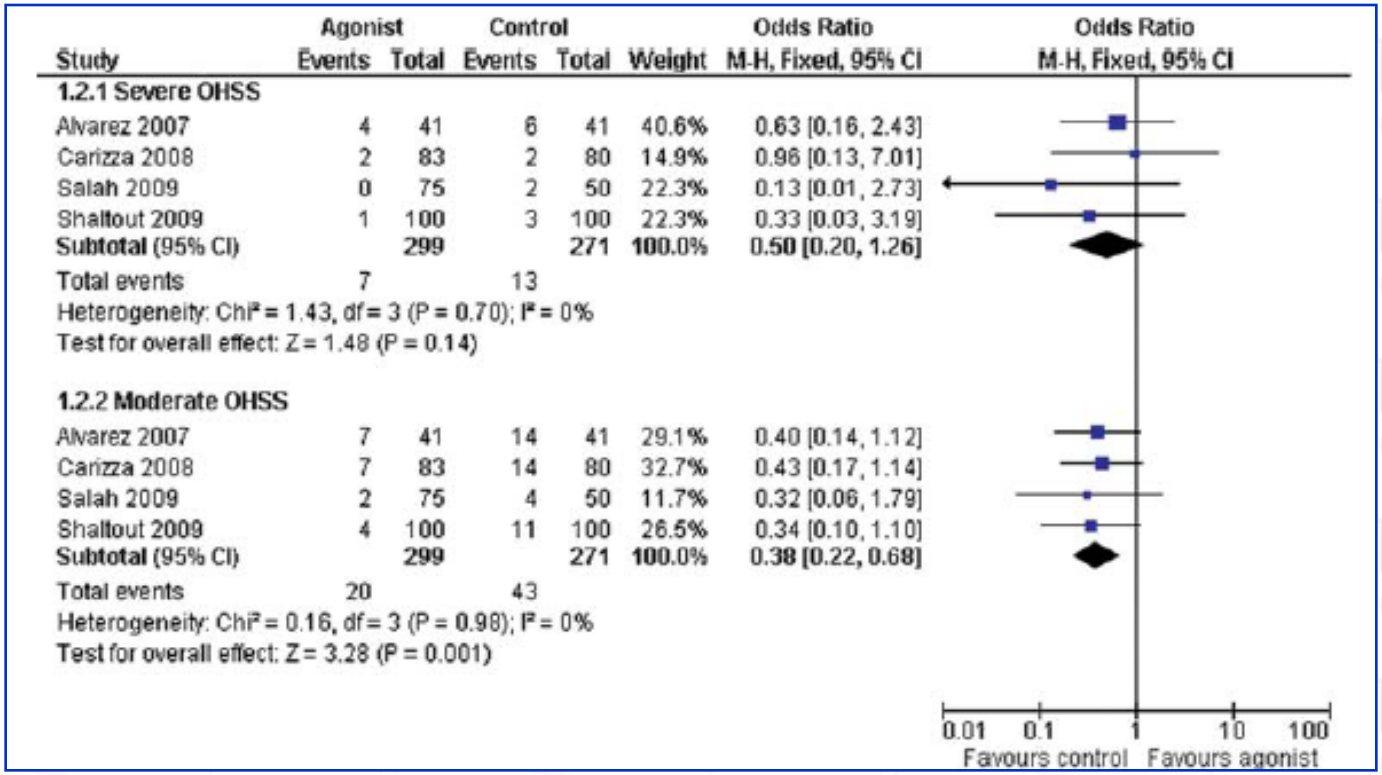
Molecular mechanism of DA on Vascular Permeability



human reproduction update

Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis

Mohamed A.F.M. Youssef[1,2*], Madelon van Wely[2], Mohamed Ahmed Hassan[1], Hesham Gaber Al-Inany[1], Monique Mochtar[2], Sherif Khattab[1], and Fulco van der Veen[2]



Significantly lower OHSS incidence in high-risk patients, without compromising pregnancy outcomes

Adjuvant Therapies

Prophylactic albumin administration at OR

Clear benefit from IV albumin at OR in preventing occurrence of severe OHSS in high risk cases(OR 0.28, 95% CI 0.11 to 0.73)

THE COCHRANE COLLABORATION®

Hydroxyethyl-starch:(HAES)

Significantly increases intravascular volume, therefore raising osmotic pressure

Serum half-life of 10 h

No anaphylaxis or risk of transfer of infections

Inhibits platelet aggregation

Beneficial effect in decreasing OHSS *Graf et al., 1997, KoEnig et al.,1998, Gokmen et al.,2001*

Immunoglobulin:

Severe OHSS ⟶ low IgG, IgA gamma globulins

IV gamma globulins reduce the severity

Corticosteroids:

100 mg IV hydrocortisone after OR and followed orally

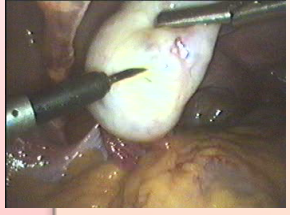
Prospective RCT did not reduce the OHSS rate *Tan et al., 1992*

Administration of methylprednisolone 16 mg per day, starting on day 6 of and tapered by day 13 after ET was effective in significantly reducing OHSS rate (10%) as compared with 43.9% in control group *Lainas et al. 2003*

Adjuvant Therapies

Prospective RCT showed significant reduction in the incidence of OHSS with LOD

Rimington MR, Walker SM, Shaw RW; Egbase PE , Fukaya et al., 1995; Herve Fernandiz, 2011



LOD did not demonstrate significant differences in LBR and ongoing pregnancy rate, miscarriage or OHSS rates

THE COCHRANE COLLABORATION®

THE COCHRANE COLLABORATION®

Metformin

Risk of OHSS was significantly decreased in women with PCOS undergoing IVF or ICSI cycles, with a trend for decreased serum E2 levels

Aspirin

Reduced incidence of severe or critical OHSS in GnRH agonist long protocol 100 mg/d aspirin from day 1 of cycle (2/780 vs 43/412 p<.001)

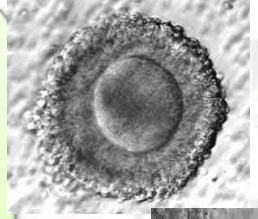
Varnagy et al (2009) Fertil Steril

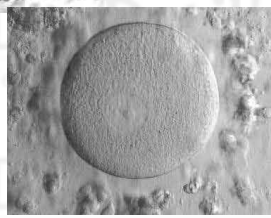
Other Therapies

In – Vitro Maturation of Oocytes

in PCOS patients ,OHSS could be prevented by minimal stimulation and IVM *Child et al., 2001*

Not achieved PRs comparable to conventional IVF*Chan et al., 2003*





Follicular aspiration

Effect Controversial

Reduces the incidence and severity

Coskun S, Whelan JG 3rd, Egbase P E et al Laufer et al., 1990

Does not prevent OHSS

Aboulghar et al., 1992;Egbase et al., 1998

Luteal phase support

Avoid hCG, Use P4

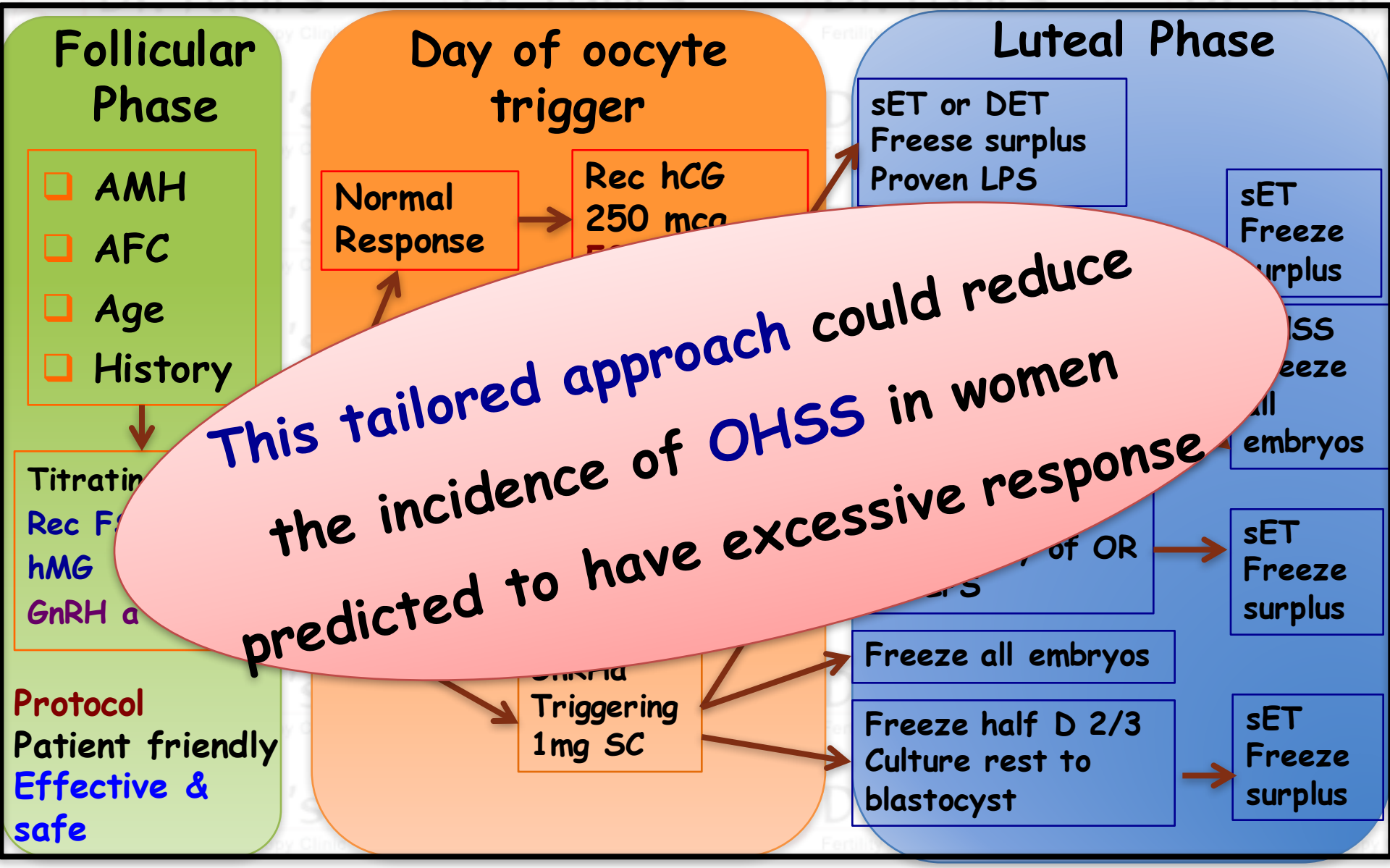
[Evidence level 1a]

Ludwig M, Diedrich K

Interventions that do not reduce the risk of OHSS

Intervention	Grade of evidence
Intravenous Albumin	A
Follicle aspiration prior to hCG	A
Rec LH instead of hCG	A
Rec hCG instead of urinary hCG	A
One type of FSH versus another	A

Individualization of Protocols to reduce OHSS



Conclusion - Prevention

Before

Identific… factors to …

Correct … stimulati…

Use … ant…

Cycle cancellation or Coasting

During

embryo ↓ MPRate thus OHSS

After

…on of all …ansfer in …cycle

…terone …G for …

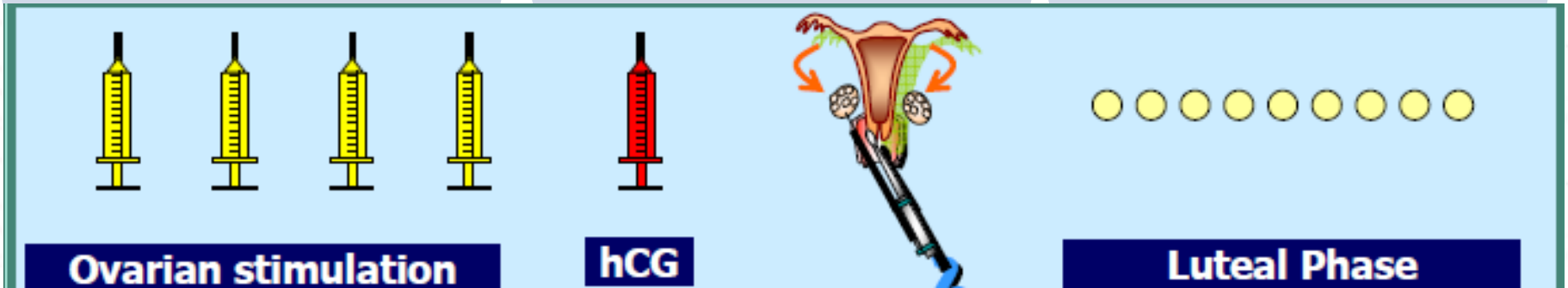
…nist post …g all embryos or with Fresh ET?

In the past apart from cancellation, none of the approaches were totally efficient, although they decrease the incidence in patients at high risk of OHSS

HCG is primary stimulus for the syndrome

Withholding hCG is the main preventive measure

…cycle with cryopreservation all embryos to be transferred in subsequent cycles



Take home message

GnRH antagonist protocol coupled with GnRHa triggering

Best method of preventing OHSS in oocyte donors also

Take home message

However, GnRH agonist trigger leads to lower luteal phase steroidal concentrations

LP and early pregnancy support with adequate E2 and P4 supplementation is essential for optimal outcome

Single blastocyst transfer is strongly recommended

LPS with low doses of hCG in high risk patients, secure a normal pregnancy outcome

Significantly higher rate of early pregnancy loss in the GnRHa group

The Ultimate Goal of ART:

A Single

Healthy

And

Happy Baby


Thank You
Dr. Madhuri Patil